Metal Catalysed Acyl Transfer Reactions of Amides

Atkinson, Benjamin

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Benjamin Nicholas Atkinson

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Contents

Abbreviations

µL	Microlitre
acac	Acetylacetonate
Anhydr.	Anhydrous
Ar	Aryl
a^{TM}	Coordination ability towards a transition metal
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
*n*Bu	Butyl
CAL	*Candida antarctica* lipase
calcd	Calculated
CCL	*Candida cylindracea* lipase
CCl_4	Carbon tetrachloride
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
1,2-DCE	1,2-Dichloroethane
DCM	Dichloromethane
DIB	(Diacetoxyiodo)benzene
DIF-	
DMA	*N*,*N*-Diisopropylformamide dimethylacetal
DIPEA	*N*,*N*-Diisopropylethylamine
DMAC	*N*,*N*-Dimethylacetamide
DMAP	4-(*N*,*N*-Dimethylamino)pyridine
DMEDA	*N*,*N'*-Dimethylethylenediamine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
equiv.	Equivalents
ESI-TOF	Electron spray ionisation - time of flight
Et	Ethyl
EtOAc	Ethyl acetate
GC/MS	Gas chromatography/ Mass spectroscopy
h	Hours

*n*Hept	Heptyl
*n*Hex	Hexyl
HMDS	Hexamethyldisilazane
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectroscopy
IPA	Isopropyl alcohol
M	Molar
Me	Methyl
MeCN	Acetonitrile
mg	Milligrams
MHz	Megahertz
mL	Millilitre
MS	Molecular Sieves
MTBE	Methyl tertiary-butyl ether
NMR	Nuclear magnetic resonance
o	Ortho
OAc	Acetate
^{o}C	Degrees centigrade
OMs	Methanesulfonate
OTf	Trifluoromethanesulfonate
p	Para
Ph	Phenyl
PhMe	Toluene
ppm	Parts per million
*n*Pr	Propyl
py	Pyridine
rt	Room temperature
t	Tertiary
TBDMS	Tertiary butyl dimethylsilane
THF	Tetrahydrofuran

Acknowledgements

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Abstract

The following thesis outlines work carried out during the last three years for the development and investigation of methodologies using amides as *N*- and *O*- acylating agents.

Chapter 1 highlights the range of methodologies and protocols reported in the literature that use amides as precursors for the synthesis of both functionalised amides and esters. The introduction will highlight the range of catalysts and promoters used as well as the scope of the current methodologies. As well as this it will highlight the limitations of the methodologies so emphasising where the following research fits into these areas.

Chapter 2 presents the development of a transamidation methodology using zirconocene dichloride as a catalyst. The scope with respect to functional group tolerance is presented as well as the investigations into the mechanism of the reaction.

Chapter 3 builds on the research presented in Chapter 2 and details the development of a more catalytically active zirconocene transamidation methodology. By the addition of a catalytic additive the temperature or time required for the reaction to be carried out could be lowered. Investigations into the mechanism were also carried out highlighting the *in situ* formation of an active catalytic species.

Chapter 4 details the development of an operationally simple methodology for the *O*-acylation of alcohols using amides. Using a catalytic amount scandium triflate the substrate scope of the reaction was explored with a proposed mechanism presented based on activation of the amide.

Chapter 1: Introduction

Amide bonds are highly prevalent in both natural and synthetic materials; it is a key functional group to life on earth in the form of peptide bonds in proteins. The prevalence within medical treatments, either natural or synthetic and in agrochemicals further exemplifies the importance of the chemical moiety (**Figure 1**).

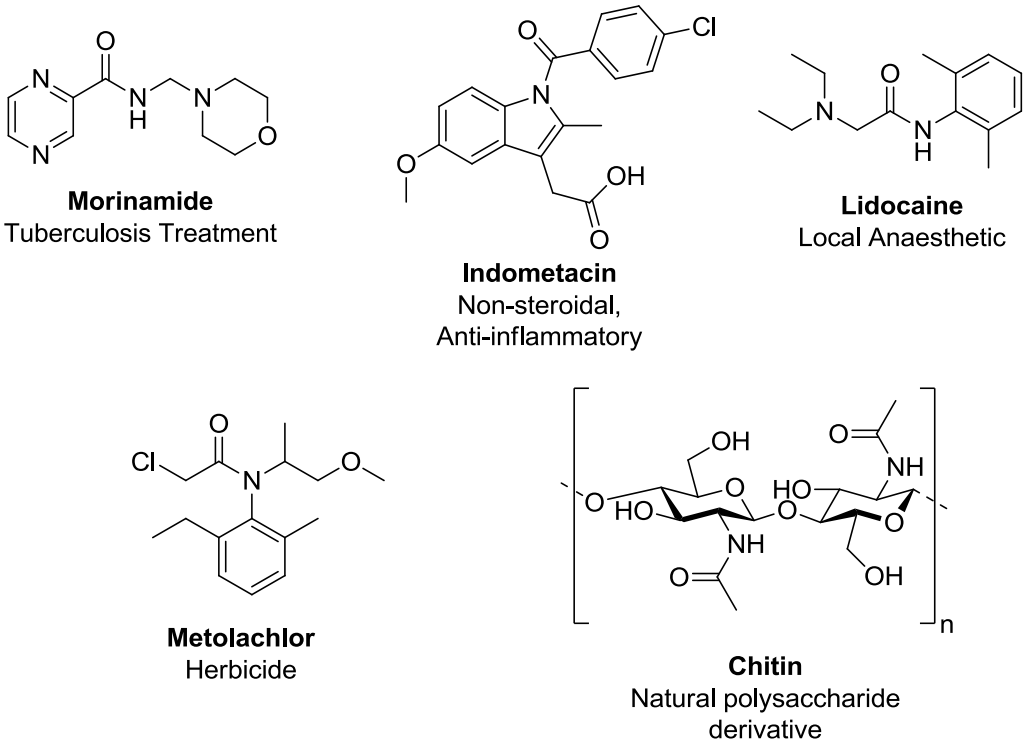


Figure 1. Amide containing pharmaceuticals, agrochemicals and natural products

Of a recent survey of 3500+ pharmaceutical compounds with available biological data, 54% were found to contain ≥1 amide moieties.[1] It was also found that 22% of the 7300+ analysed chemical reactions to synthesise these compounds were acylation reactions. 71% of these acylation reactions were amide bond forming reactions, although no differentiation is made as to whether the bond appears within the final compound or is used in forming an intermediate such as a protecting group. Other such reviews showed similar statistics for the prevalence of amides and amide bond forming reactions. They also highlight the fact that none of these analysed reactions employ catalytic amide bond forming reactions.[2] An ACS Green Chemistry Institute Pharmaceutical Roundtable vote further highlighted this as a key area of future research for greener synthetic chemistry.[3]

The high stability and relative inertness of amides often requires harsh conditions or highly evolved enzymes to react. The structure across the N-C-O bond contributes to this stability, with a large degree of co-planarity across the bond, allowing resonance stabilisation which creates a partial double bond character.[4] The use of amides as acyl donors poses an interesting synthetic challenge because of this inherent inertness.

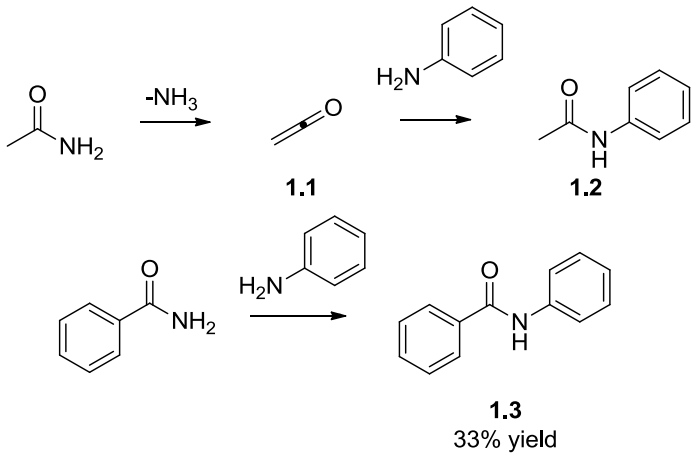
1.1 *N*-Acylation Reactions using Amides

Transamidation between amides and amines is well documented; with many different techniques and methodologies reported. The following chapter details the current reported methodologies and protocols available for transamidation.

1.1.1 Thermal Transamidation

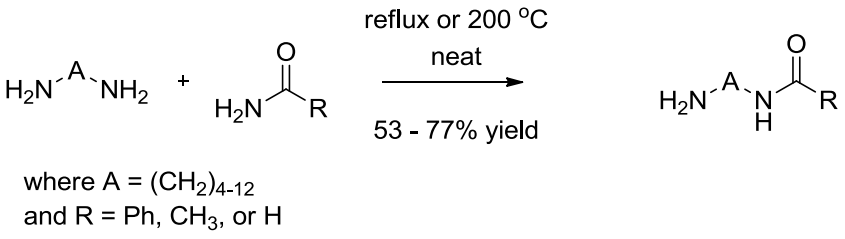
The earliest examples of transamidation involved the use of harsh conditions to push the favourable loss of ammonia from the substituting amide, as either a salt or favourable complex. One of the first examples reported the synthesis of acetanilide from acetamide and aniline.[5] Initial distillation of the aniline and acetamide mixture at 240 ^{o}C gave no conversion into anilide product. However when the acetamide was passed as a vapour through tubing at 505 ^{o}C into cold aniline it gave a mixture of acetonitrile and the desired acetanilide product in 54% and 27% yields respectively.

Higher yields of anilide product, 49%, were obtained when propionamide was used as the substrate. To gain an insight into the mechanism it was proposed that in the vapour phase the amide could undergo deammonation/elimination to give the reactive ketene **1.1**. Aniline addition across this ketene would lead to the transamidated product **1.2** (Scheme 1). Although no ketene products could be isolated or condensed before the vapour was introduced into the aniline, the ketene pathway could not be proved conclusively. The reactivity of benzamide highlighted that a mechanism *via* a ketene was not the sole reaction pathway. The corresponding anilide **1.3** was formed in 33% yield (Scheme 1). As benzamide cannot undergo the required deammonation to give the ketene, a direct acyl substitution pathway was the proposed mechanism.



Scheme 1. Deammonation of propionamide and transamidation of benzamide with aniline

The advantages of thermal transamidation are seen where standard acylation protocols can lead to large amounts of unwanted side products. This can occur in the synthesis of mono-acylated alkyl diamines, which find use as precursors for linear and cyclic-polyamines as well as pharmacophores.[6] Synthesis of these products using acid chlorides, under basic conditions (Schotten-Baumann), or other activated acyl derivatives can lead to large amounts of unwanted di-acylated product even when high excesses of the amine are used, due to the inherent reactivity of these species towards each other. When an amide and diamine in a 1:1 ratio are heated to reflux, under neat conditions, moderate to good yields are obtained of the mono-acylated product, with only small amounts of the di-acylated side product seen (Scheme 2). However the protocol is limited to diamines with boiling points >150 °C otherwise autoclave type conditions are required for the reaction to occur.

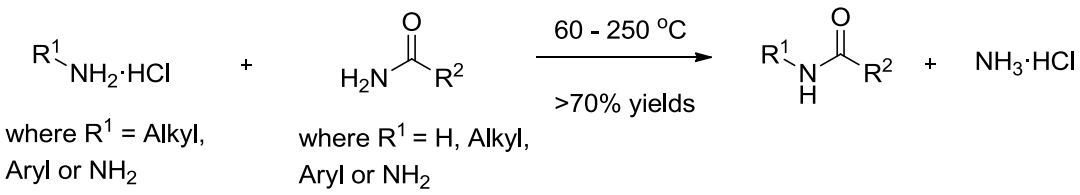


Scheme 2. Thermal transamidation synthesising mono-acylated diamines

1.1.2 Brønsted Acid Catalysed Transamidation.

Transamidation has also been performed by creating a melt of a primary amide and adding the hydrochloride or hydrosulfate salt of an amine.[7] The precipitation of

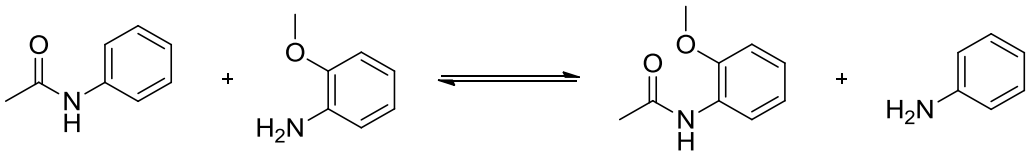
ammonium chloride or sulfate from the melt solution pushed the equilibrium towards the substituted product, but as expected high temperatures were often required to create the melt (Scheme 3).



Scheme 3. Brønsted acid promoted transamidation

Benzoic acid and butyric acid have also been shown to catalyse the thermally neutral transamidation between *o*-anisidine and acetanilide **1.2** on heating to reflux in toluene for 12 hours.[8] Acids with differing pK_a values were screened as catalysts, with no relationship between pK_a and catalytic activity noted (Table 1). A marked increase from 27% to 67% conversion into products was seen when the catalyst loading of benzoic acid was raised from 20 to 100 mol% (Table 1, entry 2). The same effect on conversion was not seen on altering the catalyst loadings of sulfuric acid (Table 1, entry 3) and a reduction was seen with higher catalytic loading of β-naphthalenesulfonic acid (Table 1, entry 4). The offered explanation was that a lower amount of free amine is present when concentrations of the stronger acids are added compared with the amount available with weaker acids such as benzoic or butyric acid.

Table 1. Brønsted acid catalysed transamidation of acetanilide with *o*-anisidine



1.2

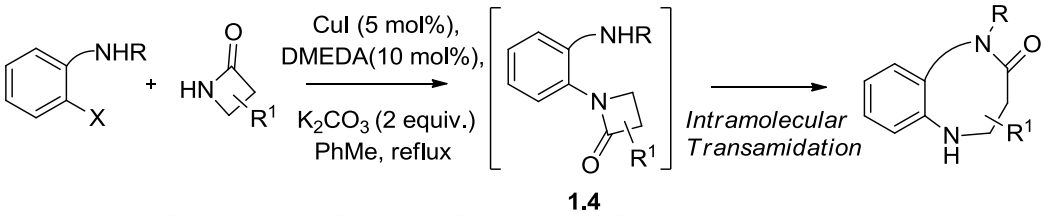
Entry	Acid	pK_a	% Conversion into 2-acetamidoanisole	
			20 mol% Acid	100 mol% Acid
1	Butyric Acid	4.8	16	48
2	Benzoic Acid	4.2	24	67
3	Sulfuric Acid	-3	43	51
4	β-Naphthalene-sulfonic acid	1.29	55	33

1.1.3 Intramolecular Transamidation

Intramolecular transamidation can be carried out without a catalyst in systems where a degree of steric strain can be relieved. Susceptibility of the carbonyl towards nucleophilic attack is increased in these strained systems due to poorer orbital overlap. The lone pair on the nitrogen has a poorer interaction with the LUMO of the carbonyl. Therefore the double bond character of the amide bond is reduced and the higher the susceptibility of the amide bond towards cleavage. This was exemplified by the uncatalysed ring expansion of a β-lactam with an intramolecular amine for synthesis of homaline.[9]

The use of β-lactams in intramolecular transamidation has also been exploited by using microwave irradiation for the synthesis of [1,4]-diazepin-5-ones.[10] Complete retention of stereochemistry in the end product can be achieved from the chirality within the starting materials. It has also found use in tandem processes where upon the completion of an intermolecular reaction, an intramolecular process then occurs leading to a variety of substituted, medium ring nitrogen heterocycles (Scheme 4).[11] 5 mol% acetic acid or 50 mol% Ti(O*i*Pr)$_4$ was used to catalyse the intramolecular transamidation with some of the more sterically hindered or lower reactivity

substrates. However in most cases the intermediate *N*-aryl lactam was only seen as an *in situ* intermediate **1.4**.

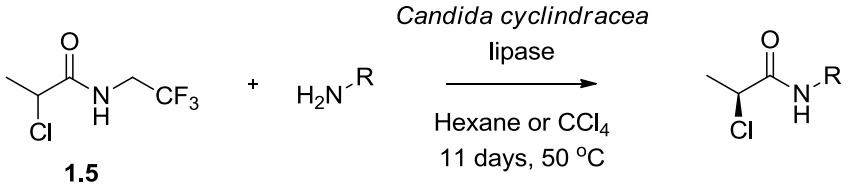


1.4

Scheme 4. Tandem coupling-intramolecular transamidation

1.1.4 Enzyme Catalysed Transamidation

Enzymes have been used to perform the transamidation process with the aim of kinetically resolving racemic amides. *Candida cylindracea* lipase (CCL) was used to kinetically resolve *N*-(2,2,2,-trifluoroethyl)-2-chloropropionamide **1.5** with aliphatic and aromatic amines.[12] However, only 3 to 48% yield of the transamidated products were obtained (**Scheme 5**). The *S*-products obtained were only moderately enantiomerically enriched, with no greater *ee* than 78% obtained over a prolonged reaction time of 11 days. As well as this a moderately activated amide was required for the reaction with 2,2,2-trifluoroethylamine as acting a stabilised leaving group relative to ethylamine, based on the difference in pK_a (5.7 *vs.* 10.7 for ethylamine). However, this demonstrated the possible use of an enzyme's active site for an asymmetric transamidation process.



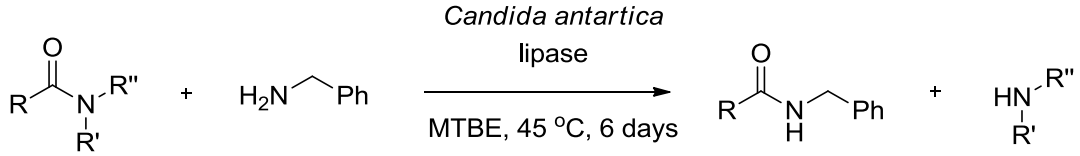
1.5

Amine Species	Isolated Yield (%)	*ee* (%)
Butylamine	48	78
Allylamine	40	60
Aniline	3	52

Scheme 5. *Candida cylindracea* lipase catalysed transamidation

Building on this lipase catalysed transamidation of secondary amides, further screens were carried out using 45 different proteolytic and lipolytic enzymes.[13] Only *Candida*

antarctica lipase (CAL, Chirazyme L-2) achieved conversion into product in the initial screen between *N*-methylpropionamide and butylamine (Scheme 6). Only sterically hindered *N*-methyl pivalamide and poorly electrophilic *N*-methyl benzamide showed no conversion into product after 6 days. Aliphatic *N*-methyl amides showed up to 81% conversion into the *N*-benzyl products (**Scheme 6**). The tertiary amide *N*,*N*-dimethylacetamide (DMAC) showed little difference in conversion compared with the corresponding secondary amide, showing the versatility of the reaction (Scheme 6). Under these conditions the authors believed an equilibrium was present, as at increased benzylamine concentrations the conversion into product was only seen to increase marginally. Increasing the reaction time to 14 days led to no significant increase in conversion, so reinforcing the argument for an equilibrium process. These conditions can also be used for the synthesis of secondary amides from primary amides, although only one example is reported with the transamidation of 2-phenylacetamide showing 100% conversion in 24 hours (Scheme 6), with the release of gaseous ammonia from solution favouring product formation.



R	R’	R’’	Conversion (%)[a]
CH_3-	CH_3-	H-	53
CH_3-	CH_3-	CH_3-	50
CH_3CH_2-	CH_3-	H-	81
$C_6H_5CH_2$	H-	H-	100[b]

[a]Determined by HPLC. [b]Reaction after 1 day

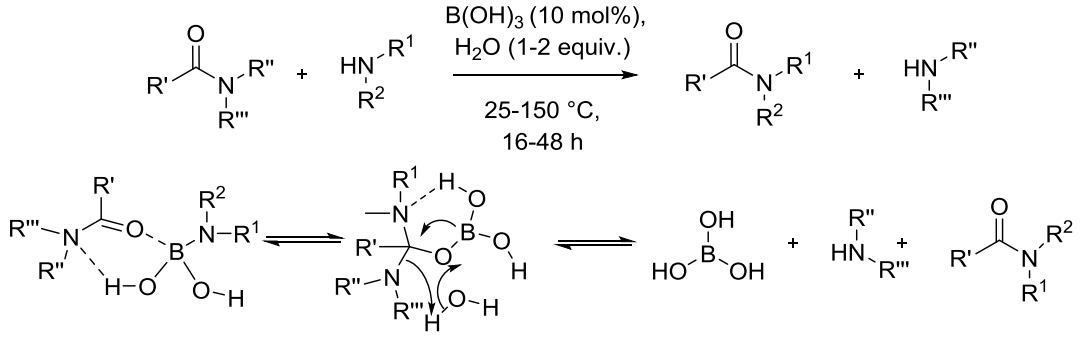
Scheme 6. Candida antarctica lipase catalysed transamidation

1.1.5 Non-Metal Catalysts

1.1.5.1 Boric Acid and Borates

Borates and boric acid have been used to promote the transamidation of primary and secondary amides. Boric esters, specifically tris(2,2,2,-trifluoroethyl)borate, has been shown to promote the reaction between primary amines and primary amides,

producing good yields of secondary amide products.[14] However two equivalents of the borate ester are required to achieve the desired products in good yields of up to 82%. Boric acid itself has been used to catalyse the transamidation of primary and secondary amides under solvent-free conditions with 10 mol% catalyst loading (Scheme 7).[15] Although this method used green, solvent-free conditions it required temperatures of up to 150 °C for >16 h to give a wide range of yields (40-90%). Due to the higher reactivity it was found that with favourable substrates, such as formamide, lower temperatures of 25 °C for 48 hours could be used. These lower temperatures were used with primary unhindered amines, however secondary, anilinic and branched amines required temperatures >100 °C to achieve reasonable yields of *N*-formylated products. It was found that one to two equivalents of water were required to promote the process, as it was speculated that it was required to regenerate boric acid in a deamination pathway (Scheme 7).

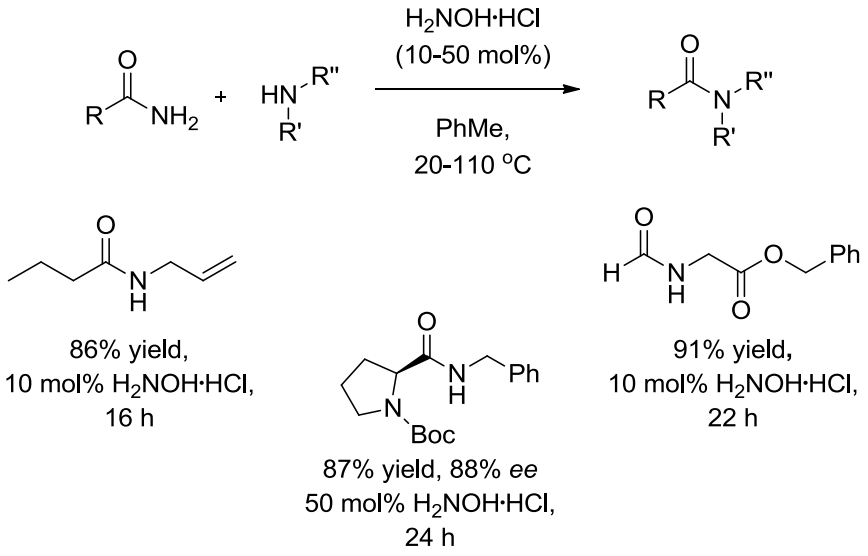


Scheme 7. Boric Acid catalysed transamidation and proposed water assisted deamination pathway

1.1.5.2 Hydroxylamine and Ammonium Salts

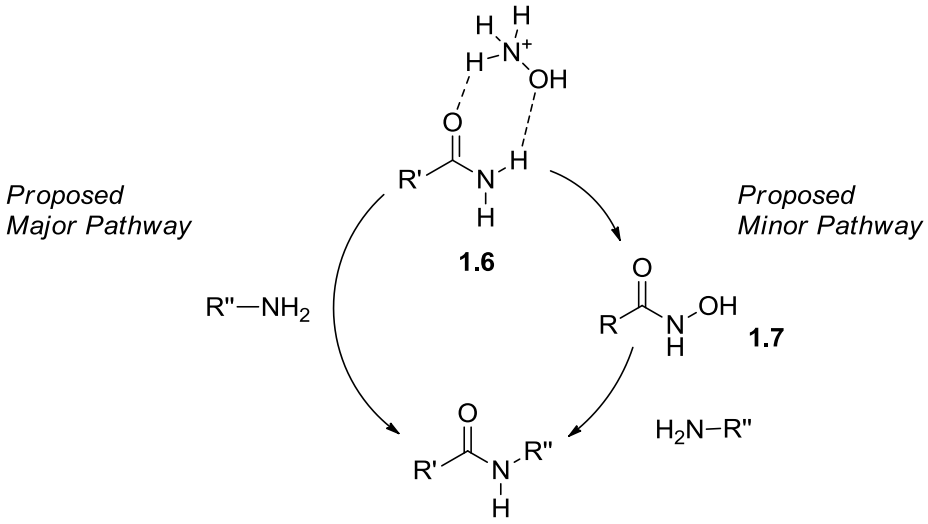
Our group has developed a transamidation process that uses hydroxylamine hydrochloride as catalyst for the transamidation of primary amides with amines (Scheme 8).[16] A variety of *O*- and *N*- substituted hydroxylamine hydrochlorides as well as hydroxylamine hydrochloride and sulfate all gave the desired secondary amide product in >73% conversion. Hydroxylamine hydrochloride was chosen as it gave 100% conversion into product as well as being cheap and readily available. It was also easily removed after the reaction *via* an aqueous workup. The reaction conditions used toluene at reflux for >18 hours and showed good substrate tolerance of halogens, heterocycles, unsaturation and protecting groups (Scheme 8). The

conditions were also shown to be tolerant to enantiomerically pure substrates, with [*N*-(benzyl)-*N'*-Boc]-L-prolinamide synthesised in 87% yield with an 88% *ee* (Scheme 8). Higher catalyst loadings of up to 50 mol%, as well as longer reaction times of up to 24 hours, were required for anilines and benzamides as well as secondary amines. The *N*-formylation of amines gave 100% conversion at only 20 ^{o}C with 30 mol% hydroxylamine catalyst, compared with a background rate of <1%.



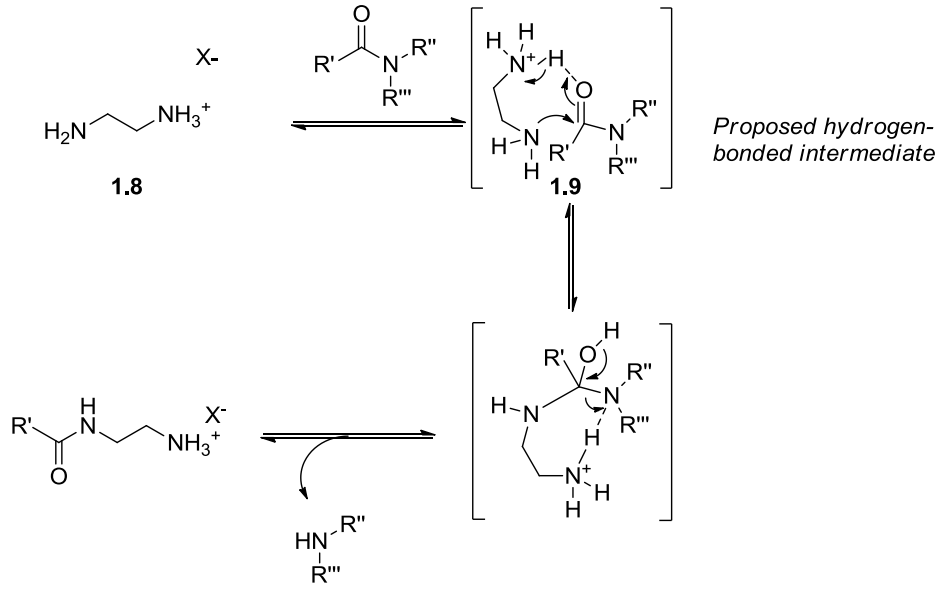
Scheme 8. Hydroxylamine hydrochloride catalysed transamidation with selected examples

Two mechanisms were proposed for the reaction (Scheme 9). The proposed major pathway (Scheme 9) was *via* a hydrogen bond activated amide **1.6** that could be nucleophilically attacked by the amine. The hydrogen bonded model was reasoned due to the observed shift of the amide NH's in the ^{1}H NMR of butyramide at 55 ^{o}C when hydroxylamine hydrochloride was added. The minor proposed pathway (Scheme 9) involved the formation of a hydroxamic acid **1.7** intermediate, which was proven to be formed under the reactions conditions without the amine present. On reaction with an amine the hydroxamic acid **1.7** produced the product in only four hours.



Scheme 9. Proposed pathways of hydroxylamine hydrochloride catalysed transamidation

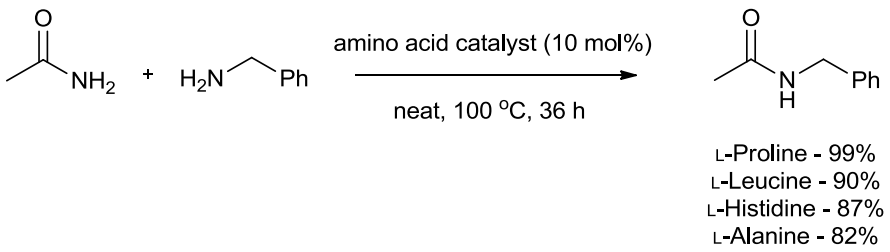
Amides are commonly used in organic reactions as protecting groups, so selective cleavage of an amide is a desirable process. Ammonium salts have been used in the transamidation of amides and diamines.[17] When the amide is viewed as an acyl protected amine release of the amine as a leaving group in transamidation provides a useful synthetic process. An *N*-acylated amine was reacted, neat, with four equivalents of 1,2-ethylenediamine in the presence of one equivalent of ammonium bromide under microwave heating. The deprotected amine can then be extracted by a simple acid-base workup, removing the formed ethylenediamine monoamide in the workup. The reported yields were >81% within 3-10 hours, with no column chromatography necessary. The methodology was compatible with a large range of functional groups including silyl, sulfonamide and alkoxy protecting groups as well as free carboxylic acids and alcohols. The supporting information proposes the formation of an ethylenediamine monohydrohalide **1.8**, shown by release of ammonia upon reaction with ethylenediamine and the ammonium halide. This was then able to interact, *via* a hydrogen-bonding mechanism **1.9**, with the amide carbonyl so increasing the electrophilicity and susceptibility to attack from non-protonated end of the ethylenediamine (Scheme 10). Crucially a difference in conversion was seen on varying the aliphatic chain length of the diamine and when pentylamine was used.



Scheme 10. Hydrogen-bond assisted deamination of amides using ammonium salts

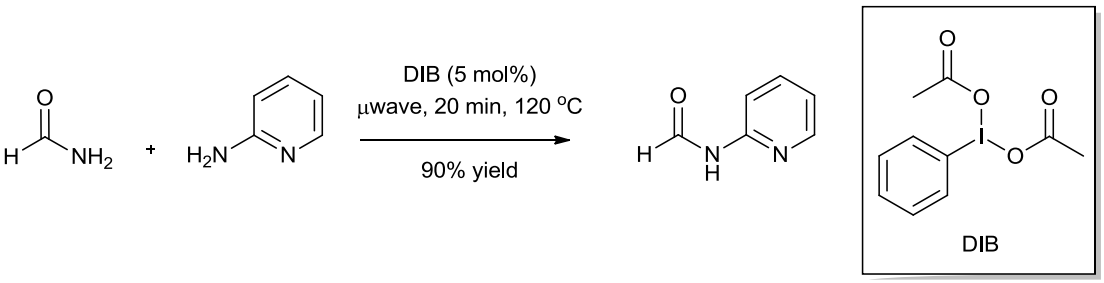
1.6 Organocatalytic Transamidation

Other transamidation catalysts have recently been reported including organocatalysts, such as L-proline[18] and benzotriazole,[19] as well as hypervalent iodine compounds.[20] Each of these brings the advantages and disadvantages associated with the classes of compounds. L-Proline as a catalyst for transamidations offers the benefits of a cheap, robust and environmentally benign catalyst.[18] It was found that under neat conditions acetamide, benzamide and phthalamide could be transamidated with alkyl and aryl amines. Only 10 mol% L-proline catalyst was required with other amino acids also showing some, albeit reduced, activity (Scheme 11). Prolonged reactions times of >30 hours and temperatures of 100 to 150 °C were required for all substrates except formamide which, as seen previously, was active at room temperature.



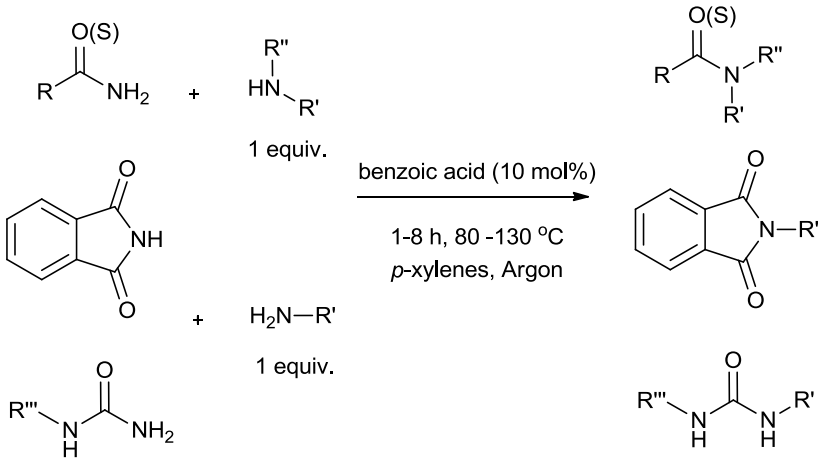
Scheme 11. Amino acid catalysed transamidation of acetamide

With microwave irradiation and under neat conditions, (diacetoxyiodo)benzene (DIB) was also been shown to catalyse transamidation reactions (Scheme 12).[20] Only 20 minute reaction times were required to produce good to excellent yields of aryl and alkyl products, compared with >16 hours under thermal conditions. However temperatures of >100 °C were required for all examples except one.



Scheme 12. (Diacetoxyiodo)benzene catalysed transamidation of formamide

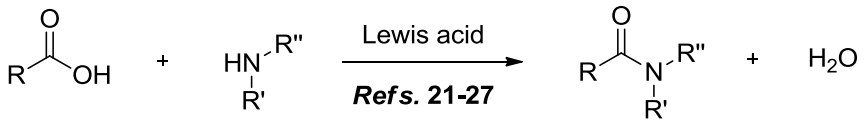
An interesting methodology has recently been reported that uses benzoic acid as a readily available and cheap organocatalyst for the transamidation reaction. Carboxylic acids, with a range of pK_a values, were tested as catalysts in the reaction between benzamide and benzylamine with benzoic acid (10 mol%) proving to be the most effective. The reaction protocol was shown to be effective not only with a range of amides and amines but also for the reaction of phthalamides, ureas and thioamides with amines. However high temperatures of 130 °C were required for the reactions to proceed and even favourable substrates such as formamide required a temperature of 80 °C. Benzoic acid, when used as the reactant under the reported conditions, showed no direct amide coupling with the amine. This was likely to be due to the reduced electrophilicity compared with aliphatic carboxylic acids, as even under Cp_2ZrCl_2 catalysed conditions low reactivity has been reported.[21]



Scheme 13. Benzoic acid catalysed reaction of (thio)amides, phthalamides and ureas with amines

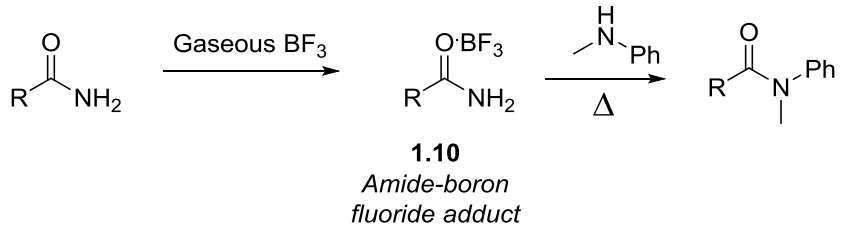
1.7 Lewis Acid Catalysed Transamidation

Lewis acids are able to activate carbonyl containing compounds to nucleophilic attack by increasing the electrophilicity of the carbonyl carbon. Within the area of amide bond formation they have been used to promote the direct coupling of a carboxylic acid and an amine (Scheme 14). A range of both non-metallic and metallic, hetero- and homogeneous catalysts promote this process including electron-rich triarylbismuthanes,[22] zinc oxide,[23] sulfated tungstate,[24] zirconium tetrachloride[25] and our own group's reported work using Cp_2ZrCl_2.[21] A comprehensive review of the area, as well as other direct amide bond forming reactions, was recently published by Adolfsson and co-workers.[26] As well as this an update on the recent advances was recently reported by Sheppard and co-workers.[27]



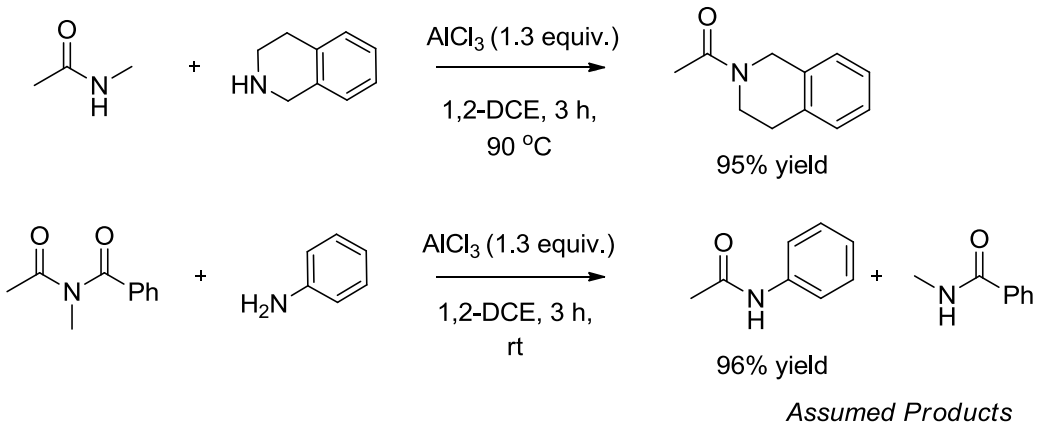
Scheme 14. Direct Lewis acid catalysed amide formation from carboxylic acids and amines

Lewis acid activation of amides has also been studied and various methods reported. The first report by Sowa and Nieuwland showed that by passing boron trifluoride (BF_3) over a primary amide, an amide-boron fluoride adduct **1.10** was formed (Scheme 15).[28] Transamidated products could then be obtained by addition of an amine and heating the mixture to reflux. The removal of ammonia in the form of ammino-borofluoride was the proposed driving force of this process. Only the reaction of primary amides with aniline and other anilinic and alkylamines was explored in this methodology. Aliphatic and *N*-methylaniline showed much lower yields with acetamide than the 99% achieved with aniline.



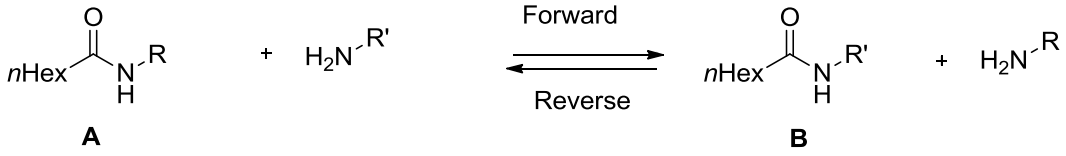
Scheme 15. Amide-boron fluoride adduct promoted transamidation

Not until 1994 were metallic Lewis acids used to promote transamidation reactions, with aluminium trichloride ($AlCl_3$) used in greater than stoichiometric amounts. The transamidation of both unactivated primary and secondary amides, as well as activated amides, with primary and secondary amines (Scheme 16) was undertaken.[29] Under these conditions secondary amides showed a greater reactivity than primary amides evident by the reaction of *N*-methyl acetamide yielding 97% in 3.5 hours with benzylamine, whereas acetamide only yielded 67% in 14 hours. Sterically hindered amides, such as *N*-methylpivalamide, and amines showed no conversion into products even when 2.3 equivalents of $AlCl_3$ were used. Activated amides such as imides (*N*-benzoyl and *N*-pivaloyl) and *N*-tosyl amides underwent transamidation at room temperature. *N*-Acetyl-*N*-methylbenzamide was transamidated using both *t*$BuNH_2$ and aniline in >96% yields and within two to three hours (Scheme 16). Although not stated categorically which amide product was produced, as the imide was unsymmetrical, it was likely that it was the *N*-acetyl product that was produced as benzamide was shown to be less reactive. Little indication as to a mechanism was given however a tentative mechanism involving chloride displacement on the aluminium, forming an active aluminium-chloro-amine complex, was stated.



Scheme 16. Aluminium trichloride promoted transamidation of non-activated and activated amides

The first report of transamidation using truly catalytic amounts of metal complexes was reported using tetrakis(dimethylamino)titanium ($Ti(NMe_2)_4$) and scandium triflate ($Sc(OTf)_3$).[30] A wide range of Lewis acidic metal complexes and metal amide bases, including alkali-metals, transition metals and main group metals, was screened for activity. Using *N*-phenylheptanamide, a small range of primary amines was used to give the desired transamidated product. It was noted that when chelating groups, such alkoxy groups, were present within the substrates $Sc(OTf)_3$ succeeded where $Ti(NMe_2)_4$ failed. When alkylamines were used as the nucleophile the release of the aniline leaving group provided a thermodynamic driving force for product formation. Equilibrium data was obtained for this reaction showing the low reversibility with $Sc(OTf)_3$ and $Ti(NMe_2)_4$ (Scheme 17). However when 5 mol% tris(dimethylamino)aluminium dimer ($Al_2(NMe_2)_3$) was used, an equilibrium point was reached with a 50:50 mixture of the two amides seen in both the forward and reverse reactions. An equilibrium point was also reached in the thermodynamically neutral reaction between a *N*-alkyl amide and an alkylamine on use of 5 mol% $Al_2(NMe_2)_3$ (Scheme 17). However neither $Sc(OTf)_3$ nor $Ti(NMe_2)_4$ showed any catalytic activity in this reaction (Scheme 17). Interestingly $Ti(NMe_2)_4$ achieved the same equilibrium point in the transamidation of *N*-aryl amides with arylamines (Scheme 17)with reduced activity seen with $Al_2(NMe_2)_3$ and no activity observed with $Sc(OTf)_3$ in both thermally neutral reactions (Scheme 17).

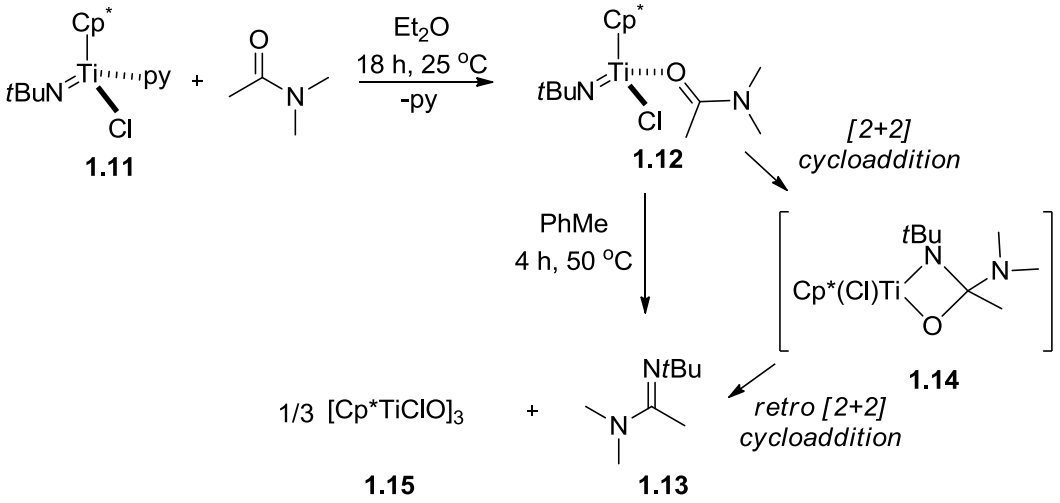


			Amide Ratio (A/B)[a]	
R	**R'**	**Catalyst**	Forward	Reverse
Ph	Allyl	$Sc(OTf)_3$	89/11	6/94
		$Ti(NMe_2)_4$	92/8	5/95
		$Al_2(NMe_2)_6$	50/50	49/51
*i*Bu	Allyl	$Al_2(NMe_2)_6$	57/43	55/45
Ph	*p*-Tolyl	$Sc(OTf)_3$	98/2	99/1
		$Ti(NMe_2)_4$	42/58	42/58
		$Al_2(NMe_2)_6$	65/35	43/57

[a] Ratio's determined by GC using an internal standard

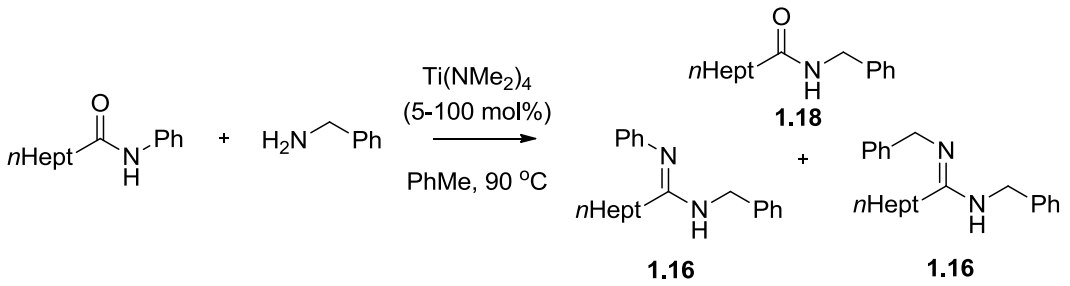
Scheme 17. Lewis acid catalysed equilibrium experiments of aryl and alkyl amides with alkyl and aryl amines

Further to this, mechanistic investigations were carried out to identify a plausible mechanism for the transamidation.[31] Initial studies were carried out in order to understand whether the reactions proceeded *via* an imidotitanium species (Ti=NR), upon displacement of a dimethylamino ligand. A preformed and well defined titanium complex with labile ligands and a *tert*-butyl imido group was used **1.11** (Scheme 18). Upon addition of one equivalent of *N*,*N*-dimethylacetamide, an amide adduct was seen **1.12** (Scheme 18). Subsequent heating to reflux did not give the transamidated product but instead the *tert*-butyl-*N*,*N*-dimethylamidine **1.13** (Scheme 18). The proposed mechanism, based on this observation, is an initial [2+2] cycloaddition of the amide to the imido-metal fragment giving a metallocycle intermediate **1.14** (Scheme 18). The formation of an oxotitanium species **1.15** (Scheme 18) is proposed as the thermodynamic driving force behind the reaction upon retro [2+2] cycloaddition of the metallocycle **1.14**.



Scheme 18. Proposed imido titanium mediated amidine formation

Variation of the catalyst loading of $Ti(NMe_2)_4$ was investigated under the same conditions as before for the transamidation of *N*-phenylheptanamide with benzylamine (Scheme 19). A noticeable change in which products were formed was seen with increased catalyst loading. Catalyst loadings of >50 mol% $Ti(NMe_2)_4$ showed more amidine formation (**1.16** and **1.17**) and very low transamidation product **1.18** (Figure 2). The reasoning was that under low catalyst loading conditions the metallocycle **1.14** (Scheme 18) that leads to the oxotitanium species is avoided, so allowing the exchange of amino fragments in the transamidation pathway. This is achieved by either direct intermolecular attack of the amine on a titanium amidate or intramolecular attack by a bound amine molecule.



Scheme 19. Transamidation of N-phenylheptanamide with benzylamine catalysed by $Ti(NMe_2)_4$

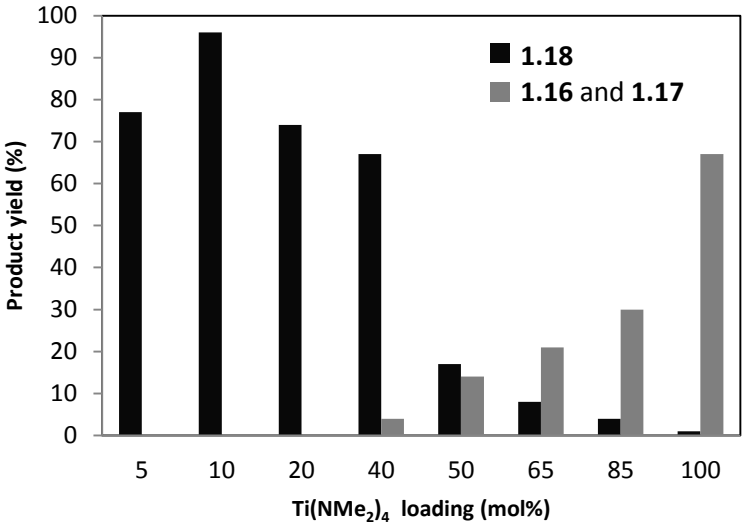
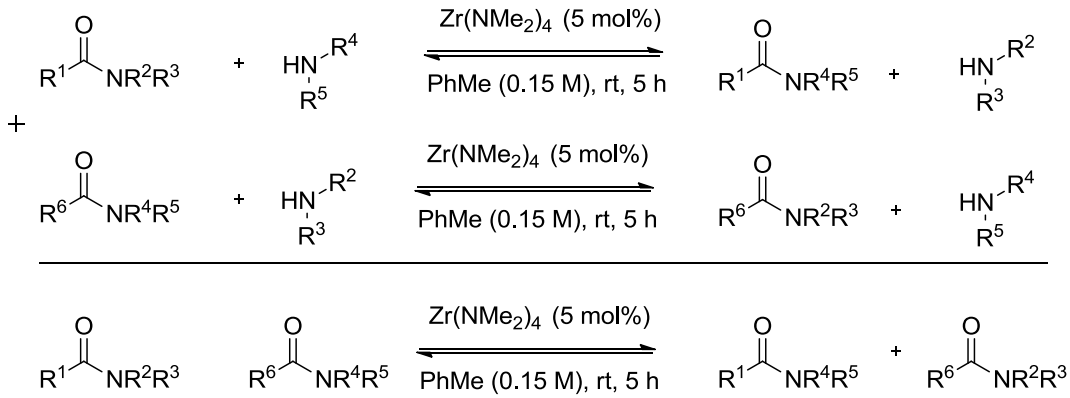


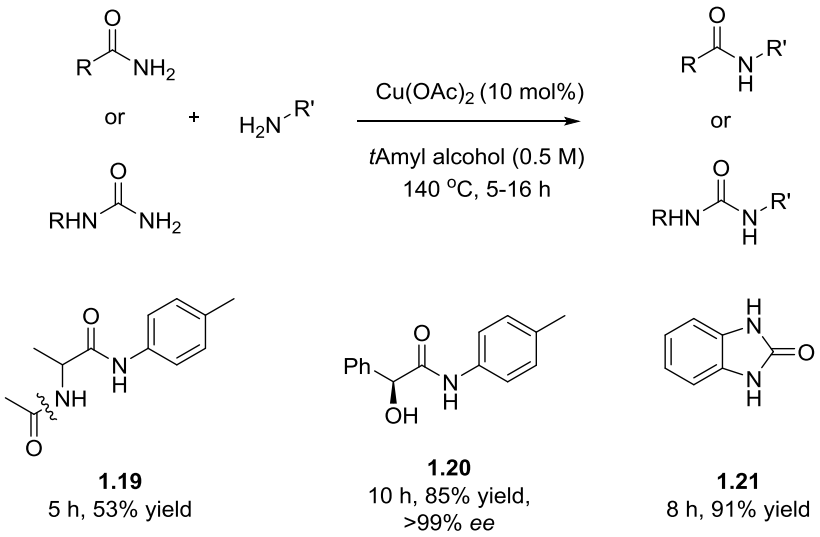
Figure 2. Product distribution with increased $Ti(NMe_2)_4$ catalyst loading

Transamidation of tertiary amides with secondary amines has also been catalysed by Lewis acids, specifically with zirconium and hafnium tetrakis(dimethylamido) ($Zr/Hf(NMe_2)_4$) complexes under ambient conditions.[32] Zirconium, hafnium as well as other previously reported catalysts such $Al_2(NMe_2)_6$ (*vide supra*) showed catalytic activity for the equilibration reactions between *N*-(4-methylbenzoyl)piperidine and *N*-benzylmethylamine in toluene at 50 ^oC. $Zr(NMe_2)_4$ was chosen due to cost considerations and was found to be active for a range of alkyl and aryl tertiary amides containing heteroatoms, halogens and alkynes at 2.5 mol% and 90 ^oC, as well as with secondary cyclic and acyclic amines containing alkenyl groups. The developed catalytic system was also found to be active for the metathesis of tertiary amides at room temperature in only five hours. The mechanism proposed involves the summation of two transamidation reactions being present within the reaction. Details are not presented as to how the amines, necessary for the two transamidation processes to occur, arise in the reaction (Scheme 20).



Scheme 20. Proposed reaction summation for amide metathesis

Copper salts have also been used to catalyse the transamidation of non-activated primary amides with amines.[33] Copper salts are attractive catalysts for the reaction as copper is a particularly cheap metal and has good functional group tolerance within homogeneous catalysis. The only reported case uses 10 mol% copper(II) acetate ($Cu(OAc)_2$) at 140 °C. The reaction shows reasonable functional group tolerance including secondary amides **1.19** and free hydroxyl groups as well as compatibility with both enantiomerically pure amides **1.20** and amines (Scheme 21). The catalytic system is also effective for the transamidation of both urea and mono-substituted ureas using mono and diamines, yielding synthetically useful heterocycles such as 2-benzimidazolidinone **1.21** and 2-imidazolidinone. The reaction times ranged from 5 – 16 hours with aliphatic amines only requiring five hours, likely due the greater nucleophilicity compared with anilines. No mechanistic investigations were reported using $Cu(OAc)_2$ as a catalyst; however a mechanism showing $Cu(OAc)_2$ as a precatalyst to an amino-copper species is proposed. The *N*-acylated amine product was detected by GC/MS although not quantified as to whether one or multiple amines caused acetate ligand displacement, so an excess (0.3 equiv.) of the amine was used.



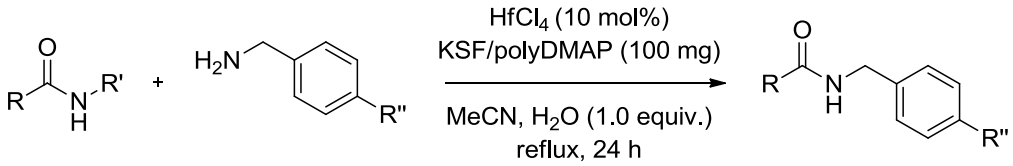
Scheme 21. $Cu(OAc)_2$ catalysed transamidation of primary amides and ureas with selected examples

The protocol does require the use of harsh conditions, 140 °C in *tert*-amyl alcohol, so heat sensitive functionalities probably would not stay intact through the reaction. Although not reported in the paper, the supporting information identifies the need for this high temperature as at lower temperatures of 110 °C only 16% conversion into products was observed.

1.1.6.1 Heterogeneous Lewis Acids

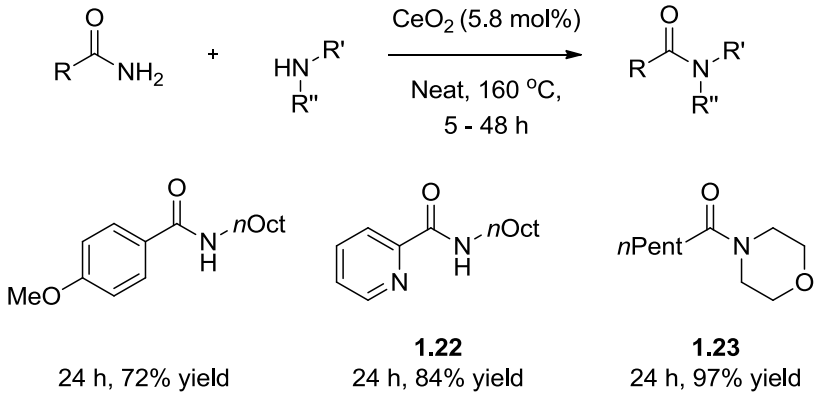
Green heterogeneous Lewis acid catalysts have been developed to catalyse transamidation reactions. The first example of which used 10 mol% of a 4-dimethylaminopyridine (DMAP) polymer supported hafnium tetrachloride ($HfCl_4$)/montmorillonite KSF catalyst (Scheme 22).[34] Heating a mixture of acetamide and benzylamine, in acetonitrile, to reflux with one equivalent of water present was found to give a 92% yield of the transamidated product. The substrate scope of the reaction was explored with primary and secondary amides, with the latter showing reduced activity but still a moderate yield of 75% was obtained. The methodology was limited to substituted benzylamines however yields of >80% were obtained. Use of allylamine in the reaction gave only 15% conversion into the *N*-allylacetamide, the major product seen was with a bis-amidine as well as other unidentified products also being produced. This highlighted a limitation in the substrate scope and although it was not explored further the catalyst loading used, 10 mol%, was reasonable high for a metal catalysed process. To compensate for this the active heterogeneous catalyst

can be recovered from the reaction by filtration and reused after drying. Only a 6% drop off in isolated yield was seen after five reuses of the catalyst, so justifying the high 10 mol% catalyst loading.



Scheme 22. Heterogeneous $HfCl_4$-KSF/polyDMAP catalysed transamidation

Other reports of recyclable heterogeneous catalysts include the use of cerium dioxide (CeO_2).[35] Under neat conditions, at 160 °C and with 5.8 mol% catalyst, a wide variety of functionalised aliphatic and aromatic primary amides were transamidated using octylamine, including pyridyl **1.22**, thiophenyl and halogenated amides (Scheme 23). Reaction times of up to 48 hours were required for some substrates, however good isolated yields >81% were obtained. The reaction was also compatible with secondary **1.23** and branched aliphatic amines, however longer reactions times were required in comparison with the aliphatic amines. Although the catalyst could be recovered and recycled up to four times without significant loss of catalytic activity the harsh conditions required, neat and at 160 °C, would not be compatible with sensitive functionalities such as some protecting groups.

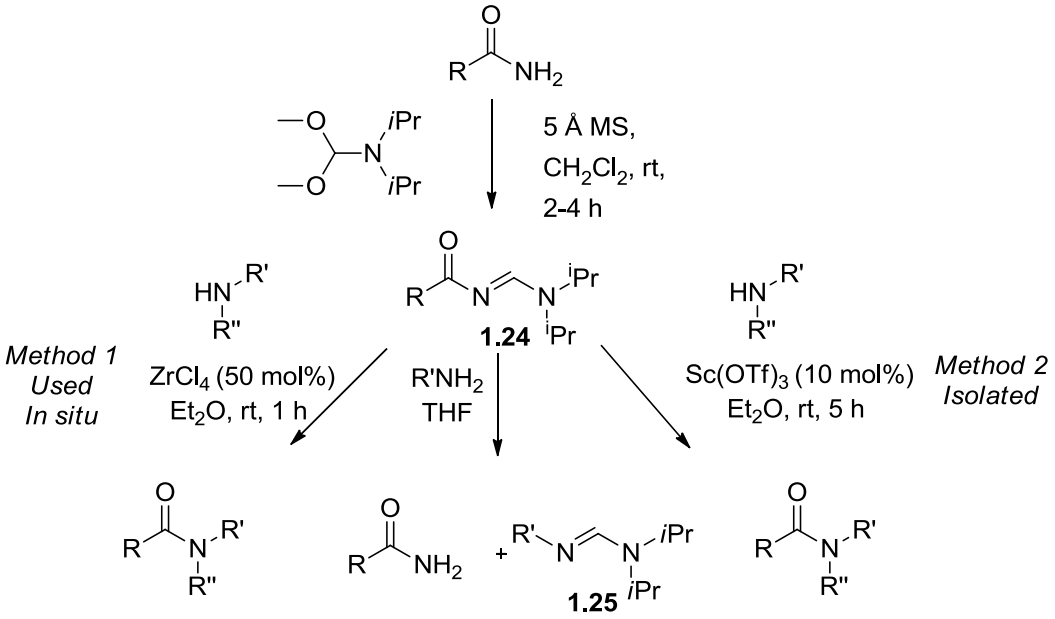


Scheme 23. Solvent-free, heterogeneous CeO_2 catalysed transamidation

More recently with 20 wt% sulfated tungstate,[36] primary amides and phthalamides could be transamidated with a range of alkyl, anilinic and amino-acid methyl esters in 12-24 hours. Formamide showed greater reactivity requiring only 20 minutes, for alkyl amines, and 120 minutes for difficult nucleophiles such as diphenylamine. Although the catalyst showed higher relative catalytic activity and functional group tolerance, with heterocycles and unsaturation, than previously reported heterogeneous catalysts it is not commercially available. Its synthesis uses hazardous chlorosulfonic acid, which may limit its application as well as create an inherent incompatibility with acid sensitive functional groups.

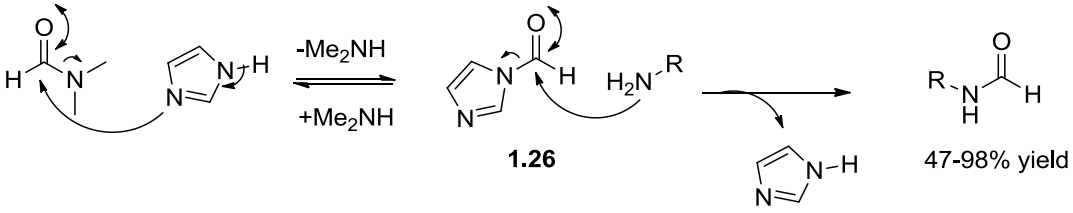
1.1.7 Organic Activation Promoted Transamidation

Activation of amides towards substitution has been carried out using stoichiometric amounts of activating agents. *N*,N-Diisopropylformamide-dimethylacetal (DIF-DMA) (Scheme 24) has been used to activate primary amides, in the presence of 5 Å molecular sieves, by forming an intermediate *N'*-acyl-*N*,*N*-diisopropylformamidine **1.24** (Scheme 24). This can act as a *N*-acyl transfer reagent towards amines so forming secondary or tertiary amides.[37] Two methods were developed to achieve this transformation (Scheme 24). The first method formed the intermediate *N'*-acyl-*N*,*N*-diisopropylformamidine **1.24** which could react *in situ* with an amine catalysed by 50 mol% zirconium tetrachloride ($ZrCl_4$). The second method involved isolation of the relatively column stable *N'*-acyl-*N*,*N*-diisopropylformamidine. Subsequent reaction with an amine in the presence of 10 mol% $Sc(OTf)_3$ yielded the transamidated product. It was found that when the formed *N'*-acyl-*N*,*N*-diisopropylformamidine **1.24** was allowed to react with benzylamine without a Lewis acid present the *N'*-benzyl-*N*,*N*-diisopropylformamidine **1.25** (Scheme 24) was formed with the primary amide regenerated. The reaction showed compatibility with a wide range of functional groups as well as compatibility with protecting groups and enantiomerically pure substrates.



Scheme 24. Transamidation using DIF-DMA activation of primary amides

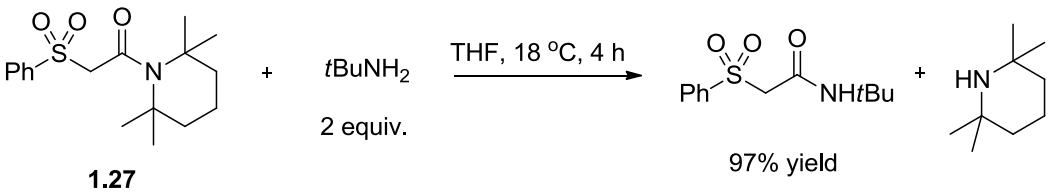
Imidazole has been used to promote the transamidation of *N*,*N*-dimethylformamide (DMF) with amino acid esters at 60 °C.[38] DMF was used as the formyl source as well as the reaction solvent and with two equivalents of imidazole present produced a range of *N*-formyl amino acid esters in 47-98% yield with no loss of enantiomeric purity. The method offers an alternative approach to the common *N*-formylating agents which are either toxic (cyanomethyl formate),[39] fairly unstable (pentafluorophenyl formate)[40] or require the use expensive transition metal catalysts (iridium).[41] The proposed mechanism involves activation of the DMF by nucleophilic substitution at the carbonyl to give *N*-formyl imidazole **1.26** (Scheme 25). Nucleophilic attack on this by the amine gives the *N*-formylated products. Lower conversions into the *N*-formylated products were achieved with other known acyl transfer catalysts such as DMAP and slower reaction times were seen when less than two equivalents of imidazole were used. This was interesting as the proposed reaction mechanism indicates it is likely to be catalytic with respect to imidazole. One equivalent is proposed to remove the stoichiometric quantity of HCl accompanying the amino acid ester and subsequently cannot take part in the reaction.



Scheme 25. Proposed mechanism of imidazole activation of formamide

1.1.8 Uncatalysed transamidation

A reported case of a neutral, room temperature transamidation involved the use of a reactive amide (Scheme 26).[42] The amide, 2-(phenylsulfonyl)-1-(2,2,6,6-tetramethylpiperidin-1-yl)ethanone **1.27** (Scheme 26), was proposed to undergo an elimination-addition type pathway in the reaction *via* a reactive ketene intermediate. This allows the reactivity of these amides to run contrary to standard acyl substitution reactions, i.e. high pK_a acyl leaving groups such as amines pK_a >30 are not otherwise displaced by lower ones such as thiophenols pK_a ~6. The transamidation proceeds at 18 °C in four hours with the leaving group of 2,2,6,6-tetramethylpiperidine as a very sterically hindered nucleophile so reducing the reversibility of the reaction.



Scheme 26. Uncatalysed transamidation of a reactive amide

1.1.9. Summary

A variety of methodologies and procedures have been developed and reported for the transamidation of amides with amines. There are still some drawbacks to the reported procedures which often involve harsh reactions conditions with high temperatures or harsh reagents, limiting the substrate scope, as well as high catalyst loadings. Although some milder conditions are reported they often involve stoichiometric amounts of activating agents or are active under milder conditions with favourable substrates displaying an inherent degree of reactivity. Other reported

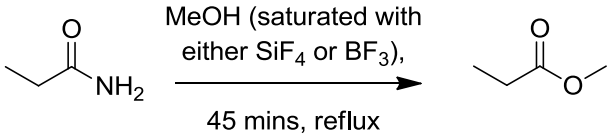
procedures are based around achieving equilibria between substrates in thermally neutral processes.

There is still a need for the development of a catalytic system for the transamidation of non-activated amides that uses milder conditions than those used previously and a simple, commercially available catalyst.

1.2 *O*-Acylation Reactions using Amides

1.2.1 Direct Amide Activation

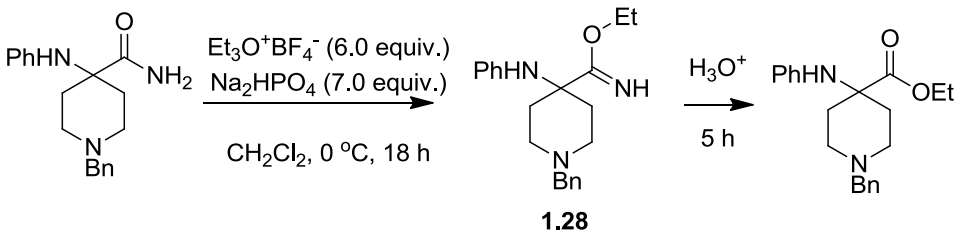
Direct alcoholysis of amides with alcohols has been carried out using three main methods. The earliest examples for the direct activation of an amide used silicon or boron fluorides. Sowa and Nieuwland showed that non-metal fluorides, specifically silicon tetrafluoride (SiF_4)[43] and boron trifluoride (BF_3),[44,28] could promote the synthesis of esters from amides (Scheme 27). However both of these conditions used highly toxic and corrosive fluoride compounds. Use of BF_3 was also exploited by Price and co-workers not only for primary amides but for the alcoholysis of disubstituted ureas.[45] However it was found that on prolonged heating, 16 hours rather than three hours, the yields of the ester products were lower. This indicated that the formed ester products decomposed on prolonged heating, with no remaining starting materials being detected.



Scheme 27. SiF_4 or BF_3 promoted amide alcoholysis

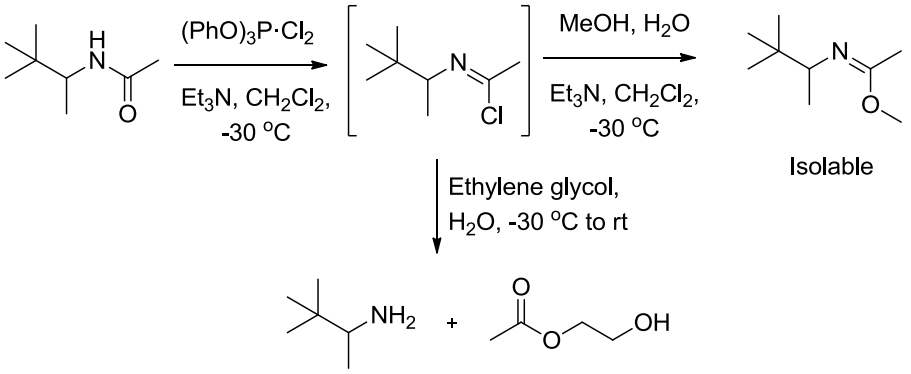
The use of tellurium ethoxide ($Te(OEt)_4$) for the synthesis of esters from amides has also been carried out. However not only is this reagent moisture and light sensitive, so requiring stringent reaction conditions, but only the ethyl ester is produced from a range of primary amides.[46] A similar lack of scope for the formed ester was seen when Meerwein's reagent was used.[47] Specifically only the methyl or ethyl esters were prepared from the corresponding Meerwein's salts *via* the imidate ester **1.28** (Scheme 28). Using these Meerwein's salts the authors were able to successfully prepare precursors for a range of analogues of the opioid Carfentanil (Scheme 28).

Other examples have used stoichiometric activating agents such as triflic anhydride[48] or amide acetals such as dimethylformamide dimethylacetal (DMF-DMA).[49] The activated intermediates, either a triflyl imidate or *N'*-acylformamidine, could then react with the alcohol to afford the ester product.



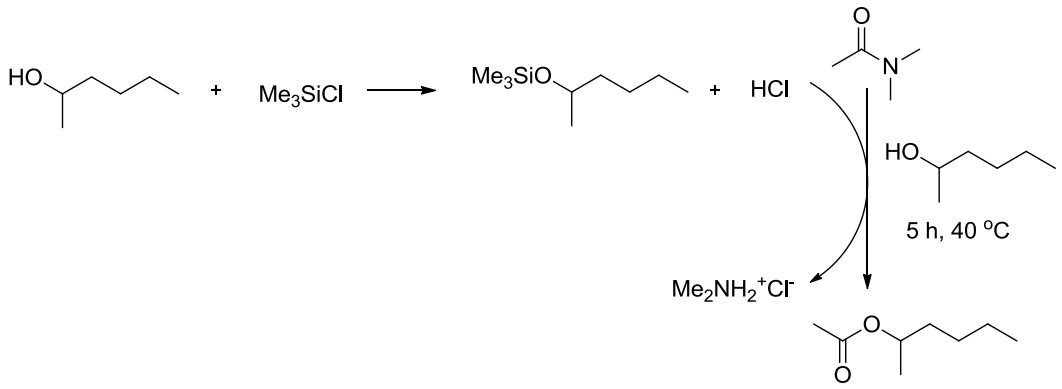
Scheme 28. Carfentanil precursor synthesis using Meerwein's reagent for amide alcoholysis

Other methods have used unique reagents to effect the alcoholysis of amides. By titrating an anhydrous solution of triphenylphosphite ($(PhO)_3P$) with chlorine gas at -30 °C a stable complex of $(PhO)_3P{\cdot}Cl_2$ was formed.[50] This complex is believed to exist as either its kinetic or thermodynamic form, though neither of these structures has been definitively determined. However both the kinetic and thermodynamic forms are observable, by ^{31}P, as a ratio and with chemical shifts different from that of the $(PhO)_3P$ starting material. The active kinetic form, seen in a higher amount than the inactive thermodynamic form, is stabilised by base. Although the research focus is on deacylation of amines with MeOH, other alcohols such as ethylene glycol were successfully used to aid the solubility of the amide. The mechanism is believed to proceed *via* an iminochloride which undergoes reaction with the alcohol to form an iminoester (Scheme 29). Subsequent hydrolysis leads to the free amine and the ester product (Scheme 29). The iminoesters were isolated in certain cases as stable products (Scheme 29). A similar method for secondary amide deprotection has also been reported however it used oxalyl chloride, with the ester produced as a by-product.[51] This method is also believed to proceed *via* an iminochloride and hydrolysis of the iminoester to give the amine and ester in an analogous manner to that using $(PhO)_3P{\cdot}Cl_2$ (Scheme 29).



Scheme 29. Iminochlorides as intermediates in the $(PhO)_3P{\cdot}Cl_2$ promoted amide alcoholysis

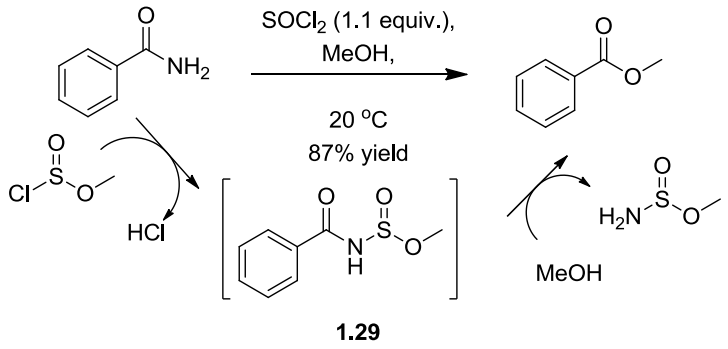
Use of or *in situ* generation of Brønsted acids have been reported to promote the alcoholysis of amides. *p*-Toluenesulfonic acid has been shown to promote amide alcoholysis, however a 4-fold excess was required for the efficient methanolysis of the Carfentanil precursor displayed in Scheme 28.[52] An interesting methodology used Me_3SiCl as a source of dry HCl for the alcoholysis of amides allowing the reaction to proceed without the problems associated with handling dry HCl gas.[53] Reaction of the alcohol solvent with Me_3SiCl forms HCl *in situ* along with the silyl ether as a side product (Scheme 30). The produced HCl then acts as the promoter for the alcoholysis reaction, with heating to 40 °C for five hours required for the reaction to proceed. The methodology was not only compatible with heteroatom containing substrates but with tertiary amides which also underwent clean reaction to give the corresponding ester products (Scheme 30).



Scheme 30. *In situ* generation of HCl from Me_3SiCl for amide alcoholysis

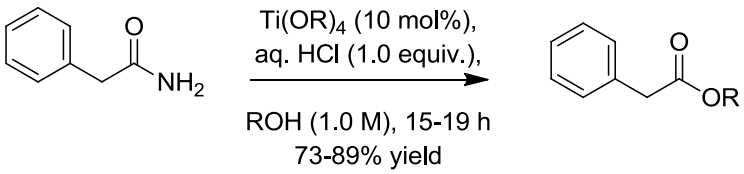
Zhu has reported a similar, operationally simple protocol but with the use of thionyl chloride as the source of anhydrous HCl. Excellent yields of methyl esters were

produced from a range of primary amides at 55 °C for six hours. Interestingly benzamide was shown to give 87% yield of methyl benzoate at only 20 °C. Although the use of a direct Brønsted acid catalysed process is suggested as a possible mechanism, DFT calculations were also carried out and showed that a mechanism involving an *N*-methoxysulfinyl benzamide **1.29** intermediate was also feasible (Scheme 31).[54]



Scheme 31. Thionyl chloride promoted methanolysis of benzamide

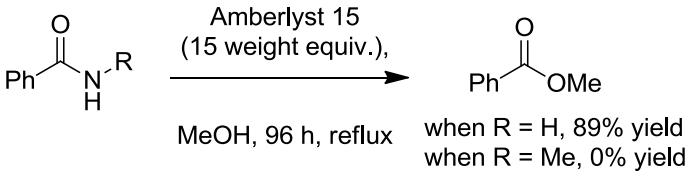
Titanium complexes have also been used for the alcoholysis of amides, however stoichiometric amounts of hydrochloric acid were required to produce the ester products.[55] The operationally simple protocol is one of the few examples that use truly catalytic amounts of metal species (Scheme 32). However being limited to low weight alcohols, as the reaction solvent, as well as stoichiometric amount of HCl highlight the limitations of this methodology.



Scheme 32. Titanium catalysed amide alcoholysis

An interesting heterogeneous method has also been reported using an acidic resin. When a primary amide was heated at reflux in methanol or ethanol in the presence of a 15-fold excess of Amberlyst 15, a polymer supported sulfonic acid based resin, amide alcoholysis was achieved. Interestingly a superb selectivity for primary amides over secondary and tertiary amides was observed allowing selective alcoholysis of primary amides in the presence of secondary amides (Scheme 33).

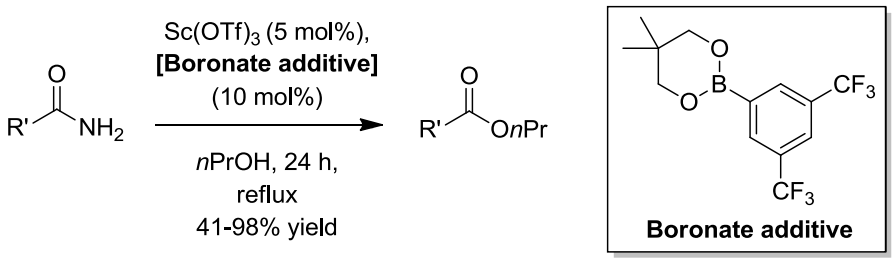
However prolonged reaction times were often required for reasonable yields of product to be achieved, with benzamide and *trans*-cinnamamide requiring 96 and 144 hours respectively.[56]



Scheme 33. Selective amide alcoholysis by Amberlyst 15 acidic resin

Siddiki has recently reported the use of CeO_2 as a reusable heterogeneous catalyst for the alcoholysis of amides. Low catalyst loadings were required for the reaction, with only 0.58 mol% of catalyst giving high yields of ester products. Although the catalyst could be recovered and reused without loss of activity, the reactions required the use of an inert atmosphere as well high temperatures of 165 °C.[57]

More recently a simple cooperative catalytic system has been developed that uses $Sc(OTf)_3$ in combination with a boronic ester for the alcoholysis of non-activated amides (Scheme 34).[14] It was shown that a wide variety of amides could be converted into their corresponding esters however the reaction required the use of the alcohol as the reaction solvent so limiting the reaction scope. Although long reaction times of 24 to 48 hours were required, good to excellent yields of ester products were obtained.



Scheme 34. Cooperative scandium and boronate ester catalysed amide alcoholysis

The proposed mechanism involves cooperative activation of both the amide and alcohol. Using NMR analysis it was seen that the scandium is responsible for direct activation of the amide as well as simultaneous activation of the alcohol through

coordination to the boronic ester (Figure 3). Lewis acids are known to increase the Lewis acidity of boron atoms *via* coordination to the bound oxygen.[58]

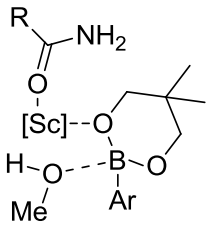
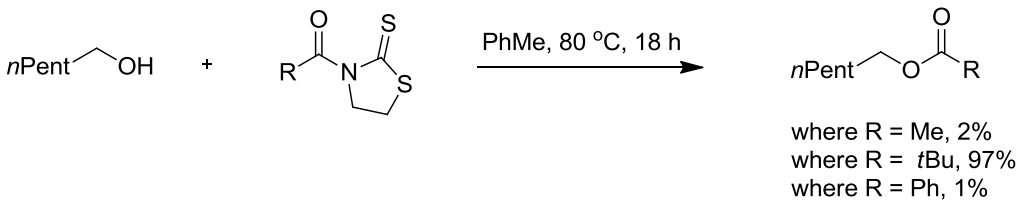


Figure 3. Proposed activation of amide and boronate by scandium with simultaneous alcohol activation

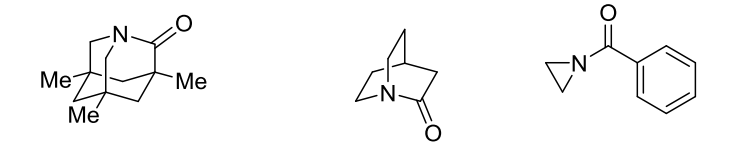
1.2.2 Use of Twisted Amides

The second method uses twisted amides to increase susceptibility of the amide to nucleophilic attack *via* disruption of the amide bond resonance. Initial methods used 3-acyl-1,3-thiazolidine-2-thiones for the selective acylation of primary over secondary alcohols.[59,60] These activated amides have been proven, by various analytical methods, to sit as twisted amides. This feature combined with the stability of the 1,3-thiazolidine-2-thione leaving group produces amides that can undergo alcoholysis under neutral conditions to produce esters selectively. An interesting observation by Yamada, was that when more sterically bulky acyl groups such as pivaloyl were used, a greater reactivity was observed in comparison with acetyl and benzoyl (Scheme **35**). This was rationalised as being due to the increased steric bulk increasing the twist across the amide bond. This resulted in decreased resonance stabilisation of the amide which is gained from the higher planarity when less sterically encumbered acyl groups are present.[60]



Scheme 35. Alcohol acylation using twisted 3-acyl-1,3-thiazolidine-2-thiones

A more recent example that has been mentioned previously (Section 1.1.8) uses sterically bulky substituents in close proximity to the amide, this in combination with electron withdrawing substituents in the β-position to the amide gave rise to amides that underwent rapid alcoholysis at room temperature.[42] Steric factors, reducing amide bond resonance, were not considered to be the sole reason of the increased reactivity. Little difference in common spectroscopic data, i.e. ^{1}H and ^{13}C NMR was seen between these amides and other less encumbered amides. It was reasoned that the steric bulk produced a lowering of the barrier of rotation of amide, with compensation for the loss of amide resonance provided by steric decompression. The proposed mechanism involved creating a transiently decoupled amide bond with transiently pyramidal nitrogen. This in combination with the decreased pK_a of the α-protons created a stabilised zwitterion *via* a proton switch. Full steric decompression and charge neutralisation would be accomplished *via* the elimination to form a ketene which could undergo rapid addition of the nucleophile. The result of which yielded ester products, not only from MeOH but from *t*BuOH and phenol in 6-24 hours.



1-aza-2-adamantanone 2-quinuclidone *N*-benzoyl aziridine

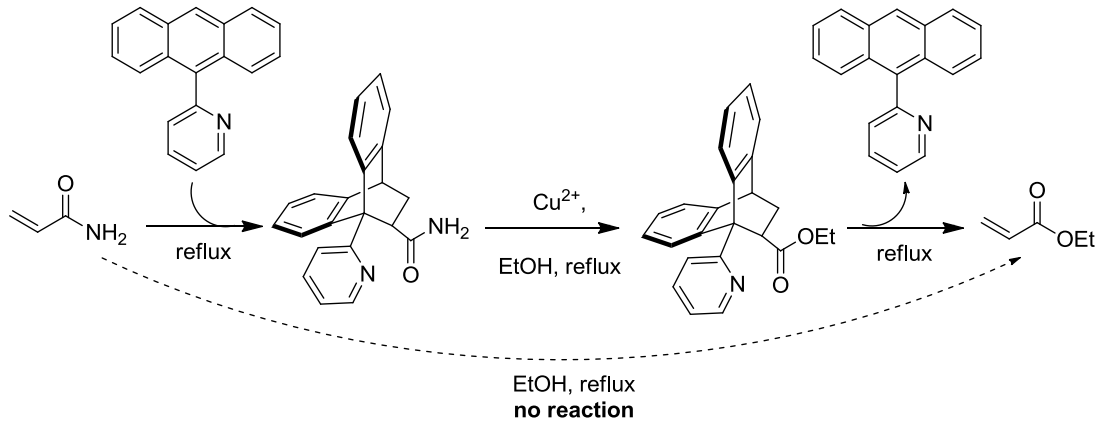
Figure 4. Reactive bridgehead amides and *N*-acyl aziridines

Other twisted amides have been synthesised that display exceptional susceptibility towards hydrolysis. Bridgehead amides display remarkable reactivity as the amide resonance is so perturbed that the carbonyl behaves very much like a ketone. Two main amides are noteworthy within the literature (Figure 4); 2-Quinuclidone[61] and Kirby's 1-aza-2-adamantanone[62]. 2-Quinuclidone was first proposed by Lukeš in 1938 and it's full synthesis not definitively carried out until 2006 by Tani and Stoltz Its free base is so unstable that it must be synthesised as it's tetrafluoroborate salt.[61] 1-Aza-2-adamantanone also displays ketone like spectral characteristics and can undergo reduction or Wittig reaction as with regular ketones.[63] Both 2-Quinuclidone and 1-aza-2-adamantanone amides undergo very fast rates of hydrolysis with half-lives of 2.48 milliseconds and <15 seconds at pH 7. Yakhontov has also shown that

these type of amides are very also susceptible to both alcoholysis and aminolysis under mild conditions.[64,65]Other unique amides susceptible to hydrolysis are *N*-acyl aziridines,[66] this is due to the structural strain placed on the amide bond by the three membered aziridine ring. The result is destabilization of the ground state allowing facile hydrolysis.

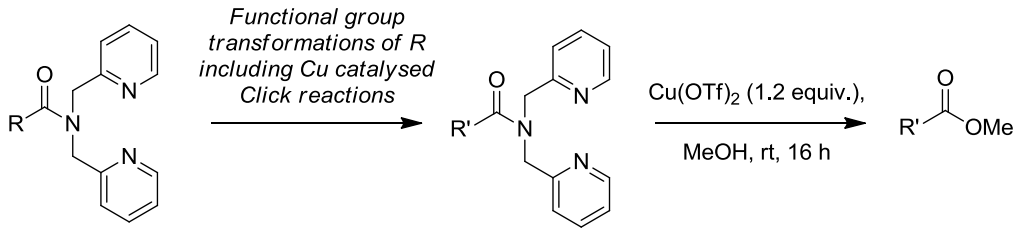
1.2.3 Directing Group Assisted Amide Bond Alcoholysis

The third method uses directing group-assisted activation of the amide bond, this ligand-like binding of an intramolecular heteroatom increases the reactivity of the carbonyl towards nucleophilic attack.[13] A number of examples have been published all reporting the alcoholysis of amide bonds either from pre-made inorganic complexes containing the amide as a ligand[67,68] or from substrate-adducts that have installed the heteroatom functionality (Scheme 36).[69]



Scheme 36. Diels-Alder adducts for the Cu^{2+} promoted alcoholysis of acrylamide

However, an interesting example uses di-(2-picolyl)-amine as a protecting group for carboxylates (Scheme 37). On addition of either 1.2 equivalents of $Cu(OTf)_2$ or $FeCl_3$, in methanol, room temperature methanolysis of amides occurred. The proposed mechanism involves coordination with the pyridyl nitrogens as well the amide nitrogen, so increasing the susceptibility to nucleophilic attack due to loss of the stabilising amide resonance.

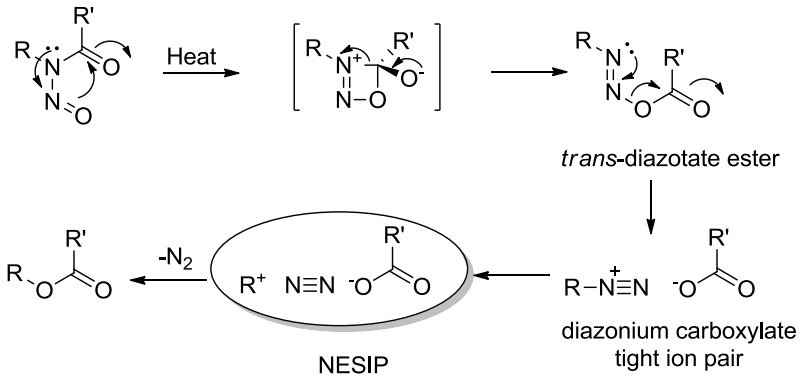


Scheme 37. Di-(2-picolyl)-amide as a carboxylate protecting group

1.2.4. *N*-Nitrosoamide Rearrangement to Esters

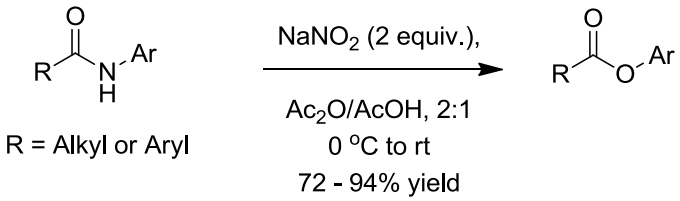
An alternative method of converting amides into ester products is by formation and subsequent rearrangement of an *N*-nitrosoamide. This method is only effective for secondary amides, however when *N*-aryl amides are used it provides an alternative synthetic route towards phenols without the need to form and subsequently decompose diazonium salts.

Hirsch, in the 1950's, reported that on heating an *N*-alkyl-*N*-nitrosoamide an *O*-alkyl ester product was produced. Extensive mechanistic investigations were carried out including the use of ^{18}O labelled products,[70,71] enantiomerically enriched starting materials as well as intermediate synthesis *via* other synthetic routes.[72] Further data on the mechanism of the reaction has been amassed more recently using NMR analysis of the reactions progress.[73] These investigations led to the following proposed mechanism (Scheme 38);[74] under heating a rearrangement of the *N*-nitrosoamide into a diazoester occurs, which is believed to be the rate controlling step. Subsequent to this it is believed that a nitrogenous entity-separated ion pair (NESIP) is formed that undergoes rapid loss of N_2 and combination of the carbocation and the carboxylate.



Scheme 38. Proposed mechanism of the thermal deamination of *N*-alkyl-*N*-nitrosoamide

The *N*-nitrosoamides were originally synthesised using gaseous dinitrogen tetroxide[75] and the deacylation was limited to *N*-alkyl *N*-nitrosoamides.[76] However more recently a simpler methodology was developed that was effective for the synthesis of *O*-aromatic esters straight from *N*-aromatic amides (Scheme 39).[77] Using a 2:1 mixture of acetic anhydride and acetic acid as the solvent and sodium nitrite as the nitroso source, high yields of esters could be synthesised in one pot from the secondary amides. Noticeably, there was consistency in the isolated yields regardless of whether electron donating or electron withdrawing groups were present. As such a radical pathway was proposed by Glatzhofer *et al.* as the formed decomposition products of an *N*-nitrosoamide were shown to act as initiators for the polymerisation of methyl acrylate.



Scheme 39. *O*-Aryl esters from *N*-aryl amides using sodium nitrite

The methodology has also been applied successfully to the deamidation of α-amino acids with complete retention of stereochemistry in the α-position.[78] Alkyl esters were successfully synthesised from the corresponding *N*-alkyl amides. However, unlike the initial publication, an *N*-aryl amide did not produce the *O*-aryl ester. Decomposition of the nitrosoamide intermediate was proposed as an explanation as the starting amide product was completely recovered.

1.4 Summary of Ester Formation Using Amides

The synthesis of ester from amides has been carried out using a variety of methods; however either a stoichiometric amount of activator and/or a tailored substrate with specific functionality was required for reaction to occur. Where catalytic methods have been developed the reaction protocol was limited to using the alcohol as the reaction solvent or requiring very high temperatures and an inert atmosphere. Therefore we chose to investigate a more general metal catalysed methodology for the synthesis of esters from amides that 1) did not require the alcohol to be used as the reaction solvent, so expanding the reaction scope and 2) would not require tailored substrates or stoichiometric amounts of an activating reagent or an inert atmosphere.

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Chapter 2 – Zirconocene Dichloride Catalysed Transamidation

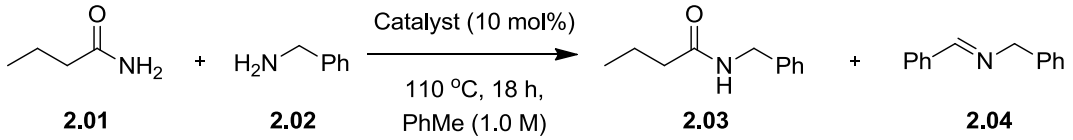
"Zirconocene Dichloride Catalysed Transamidation of Primary Amides with Amines"
Atkinson, B. N.; Chhatwal, A. R.; Lomax, H. V.; Walton, J. W.; Williams, J. M. J., *Chem. Commun.* **2012**, *48*, 11626-11628

Chapter 2: Results and Discussion I

2.1 Catalyst Identification

In order to develop a metal catalysed transamidation process it was necessary to find a suitable metal catalyst. The metal catalysts ideally had to be commercially available or easily prepared in the lab. A range of Lewis acidic metal salts and preformed metal complexes was screened for catalytic activity in a standard reaction (Table 2). A parent reaction that was 1) easily interpretable by common spectroscopic techniques and 2) successful in similar chemical transformation was chosen suing *n*-butyramide **2.01** and benzylamine **2.02**.[16]

Table 2. Metal catalyst screen



2.01 + **2.02** → **2.03** + **2.04** (*Imine Side Product*)

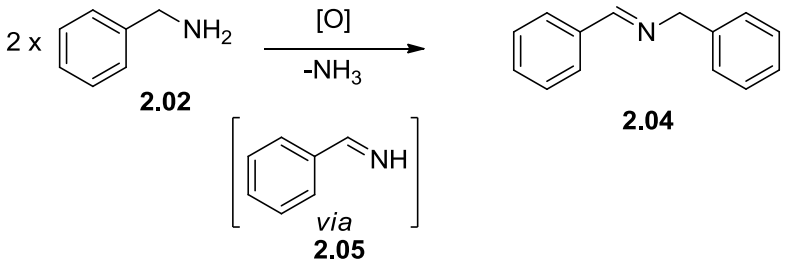
Entry	Catalyst	Conversion into 2.03 (%)[a]	Conversion into 2.04 (%)[a]
1	$AlCl_3$	54	5
2	$FeCl_2$	24	13
3	ZrF_4	49	-
4	$Co(OAc)_2$	14	31
5	$Sc(OTf)_3$	88	-
6	$ZrCl_4$	58	4
7	$ZnCl_2$	4	-
8	LiBr	4	-
9	$Ti(OiPr)_4$	75	-
10	$NiNO_3 \cdot 6H_2O$	8	-
11	$MnCl_2$	30	12
12	Cp_2ZrCl_2	100 97[b]	-
13	CuBr	-	32
14	$Zr(acac)_4$	Undetermined side-product	-

[a]Conversions were determined by analysis of the crude ^{1}H NMR spectra.

[b]Conversion after five hour reaction time.

The initial screen showed a range of catalytic activities for the different metals in the reaction of *n*-butyramide with benzylamine (Table 2). Zirconium catalysts consistently showed >49% conversion into **2.03** (Table 2, entries 3, 6 and 12), with only $Zr(acac)_4$ (Table 2, entry 14) producing an unknown side product. As mentioned previously zirconium is known to carry out the transamidation process but has only

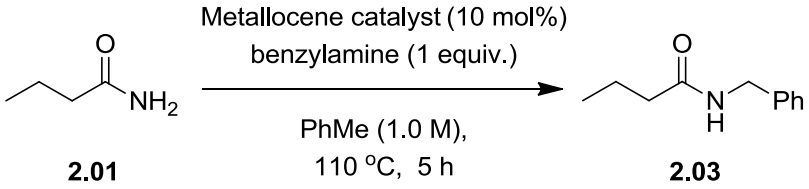
been carried out using preformed zirconium-amido complexes, requiring the use of glove-box conditions.[32] Other promising catalysts were the early first row transition metals, with Ti(O*i*Pr)$_4$ and Sc(OTf)$_3$ showing 75% (Table 2, entry 5) and 88% (Table 2, entry 9) conversion into **2.03** respectively. $AlCl_3$ also showed reasonable catalytic activity with 54% conversion into **2.03** (Table 2, entry 1). Other catalysts that were screened showed little conversion into the desired product as well as showing greater amounts of unwanted side products. Both CuBr (Table 2, entry 13) and Co(OAc)$_2$ (Table 2, entry 4) showed significantly more of the homo-coupled imine side product **2.04** than desired amide product **2.03**. The believed mechanism involves oxidation of the benzylamine **2.02** to the benzylidene **2.05** (Scheme 40) with subsequent attack from another molecule of benzylamine **2.02** to give *N*-benzylbenzylidene **2.04** (Scheme 40).



Scheme 40. Oxidative homo-coupling forming N-benzylbenzylidene

Cp_2ZrCl_2 was chosen for further use as it was the only catalyst to achieve 100% conversion into product **2.03**. It was noticed that a reduction in the reaction time, down to five hours, still gave a high conversion of 97% into product **2.03**. Following on from this, investigations were carried out as to whether catalytic activity was maintained throughout other group 4 and group 5 metallocene dichlorides (Table 3)

Table 3. Metallocene Screen



2.01 **2.03**

Entry	Catalyst (10 mol%)	Conversion into 2.03 %[a]	Cost (£/mmol)[b]
1	Cp_2TiCl_2	36 (5)[c]	0.59
2	Cp_2ZrCl_2	97	0.88
3	Cp_2HfCl_2	96	6.59
4	Cp_2NbCl_2	5	36.04[d]

[a]Conversions were determined by analysis of the crude ^{1}H NMR spectra.

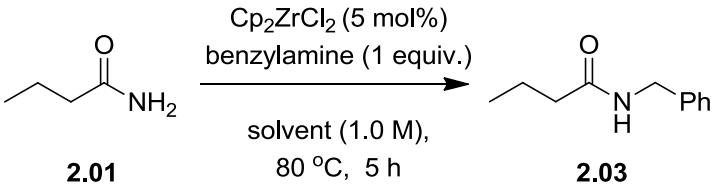
[b]Price for 25 g from Strem. [c]Conversion into imine **2.04**. [d]Price for 500 mg from Aldrich

Using Cp_2TiCl_2 as the catalyst showed not only low conversion into **2.03** (Table 3, entry 1) but 5% conversion into imine **2.04**. Interestingly use of Cp_2HfCl_2 (Table 3, entry 3) showed equivalent conversion into **2.03** when compared with Cp_2ZrCl_2 (Table 3, entry 2). This result is explained by the fact that hafnium organometallic chemistry often parallels that of zirconium.[79] However upon comparison of the costs of the catalyst it was seen that Cp_2HfCl_2 was over 6 times more expensive per mmol than Cp_2ZrCl_2 (Table 3, entry 2). Niobocene dichloride (Cp_2NbCl_2) was also tested for catalytic efficiency; however it showed little catalytic activity. This could be rationalised as niobium is a group 5 transition metal so the otherwise empty valence orbital of the group 4 metallocene complexes will be occupied by a d1 electron. It is likely that an initial interaction of the amine or amide with Cp_2NbCl_2 will be disfavoured due to the interaction of the amine lone pair with half filled valence orbital.

2.2 Solvent Screen

The reaction conditions from which the Cp_2ZrCl_2 was identified as a catalyst for transamidation, were the same as previously used within the group using hydroxylamine hydrochloride as a catalyst.[16] However when they were applied to a metal based catalytic system both the catalyst loading and the temperature were quite high. A screen of solvents, at a lower temperature and catalyst loading (80°C and 5 mol% respectively) was carried to determine if catalytic activity was maintained (Table 4).

Table 4. Solvent screen



2.01 **2.03**

Entry	Solvent	Conversion into 2.03 (%)[a]
1	PhMe	14
2	MeCN	7
3	Chlorobenzene	17
4	1,2-DCE	7
5	1,4-Dioxane	3
6	DMSO	16[b]
7	EtOH	1
8	Cyclohexane	63
9	Pyridine	9

[a] Conversions were determined by analysis of the crude ^{1}H NMR spectra.
[b]39% Imine **2.04** was formed.

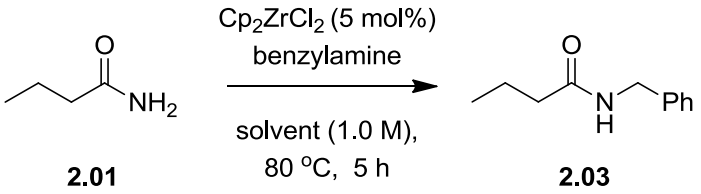
A solvent screen showed interesting results for the catalytic system, with very low conversions into product **2.03** for all solvents except cyclohexane which showed 63% conversion (Table 4, entry 8). A large difference in conversion was seen between cyclohexane (Table 4, entry 8) and the next best solvent, chlorobenzene (Table 4, entry 3), which showed only 17% conversion. Further to this, little difference was seen with other solvents including chlorinated (Table 4, entry 4), polar non-protic (Table 4, entries 2, 5, 6 and 9) and non-polar aromatic solvents (Table 4, entry 1). In some cases catalytic activity was completely shut down, such as EtOH, which showed only 1% conversion (Table 4, entry 7). In other instances unwanted side products, including imine **2.04**, were produced to greater extent than the desired product, notably with DMSO (Table 4, entry 6).

Cyclohexane was used as the solvent for further reactions, as optimal conversion into product **2.03** was shown. Ammonia likely acts a leaving group upon substitution of an attacking amine; the significantly low polarity of cyclohexane could cause a favourable loss of ammonia from solution. Although ammonia's solubility is moderately low within solvents used in other transamidation reaction conditions, such as toluene, ammonia has an even lower solubility within aliphatic hydrocarbon solvents.[80] This difference could provide an equilibrium shift that favours the products, so facilitating the reaction at a lower temperature than in toluene.

2.3 Optimisation

An initial 63% conversion into **2.03** was promising (Table 4, entry 8), however further experiments were undertaken to optimise the reaction conditions to allow near quantitative conversion into product (**Table 5**).

Table 5. Transamidation optimisation



2.01 **2.03**

Entry	Solvent	Benzylamine equiv.	Conversion into 2.03 (%)[a]
1	Cyclohexane (Anhydr.)	1.0	73
2	PhMe (Anhydr.)	1.0	27
3	Cyclohexane (Anhydr.)	1.2	100
4	Cyclohexane	1.2	81
5	1:1 – Cyclohexane (Anhydr.): PhMe (Anhydr.)	1.0	69

[a] Conversions were determined by analysis of the crude ^{1}H NMR spectra.

Zirconium and related high valence, early transition metal chlorides are known to undergo hydrolysis to oxides due to their inherent oxophilicity.[81] Adventitious water present within the solvents used or within the reaction vessel, could have caused some loss of catalytic activity due to the formation of zirconium oxides. When a nitrogen charged reaction vessel and anhydrous cyclohexane were used, an increase in conversion to 73% (Table 5, entry 1) was observed. A similar increase in conversion from 14% (Table 4, entry 1) to 27% (Table 5, entry 2) was seen when these anhydrous conditions were applied with toluene as the solvent.

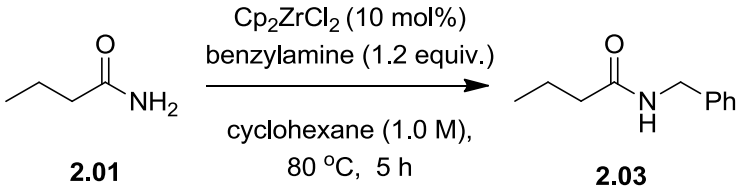
If the amine nucleophile was substituting for a chloride upon the catalyst, theoretically 10 mol% hydrochloric acid could have been produced. The amine present within the reaction subsequently would act as a base, forming the hydrochloride salt. Only 90% of the added amine would then be able to act as a nucleophile. In order to increase the conversion into product **2.03**, the quantity of amine nucleophile was increased to compensate for this process. A further increase to 81% conversion was noted (Table 5, entry 4) with 1.2 equivalents of benzylamine, compared with *n*-butyramide **2.01**, were used without the anhydrous conditions.

When 1.2 equivalents of benzylamine were used, under the same anhydrous conditions as previously noted, 100% conversion into product **2.03** was achieved within five hours (Table 5, entry 3). Also of note was the use of a 1:1 ratio of cyclohexane: toluene (Table 5, entry 5) that showed an increase to 69% conversion in comparison with 27% conversion in toluene alone (Table 5, entry 2). This further highlighted the significance of carrying out the reaction in aliphatic hydrocarbon solvents, as even a mixture produced a significantly increased conversion.

2.4 Control Reactions

In order to determine whether Cp_2ZrCl_2 was having a true catalytic effect or whether a change of solvent or a by-product formed was catalysing the reaction, it was necessary to carry out control reactions (**Table 6**).

Table 6. Control reactions



Entry	Catalyst (10 mol%)	Conversion into 2.03 (%)[a]
1	-	8
2	$BnNH_2 \cdot HCl$	5
3	NH_4Cl	5

[a] Conversions were determined by analysis of the crude ^1H NMR spectra

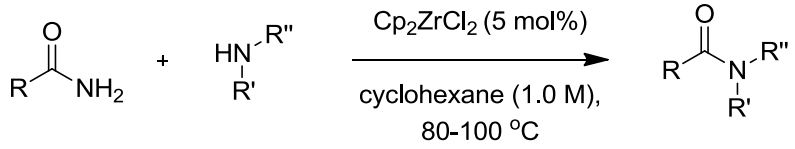
The uncatalysed reaction, under the optimised conditions (Table 6, Entry 1**)** gave 8% conversion into product **2.03**, so ruling out the change of solvent and conditions as the sole cause of the reaction. The use of hydrochloride (10 mol%), in the form of benzylamine hydrochloride, gave only 5% conversion into products (Table 6, entry 2), so removing the likelihood of a solely Brønsted acid catalysed process. A similarly low conversion of 5% (Table 6, entry 3) was seen with ammonium chloride (10 mol%) which could also be produced by the reaction of ammonia and HCl by-products.

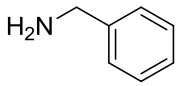
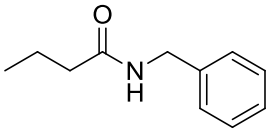
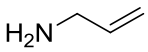
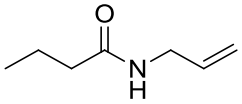
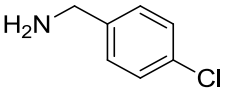
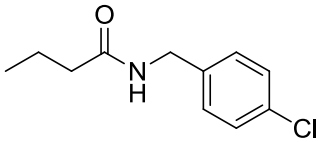
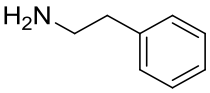
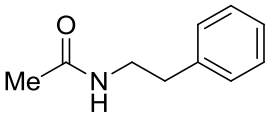
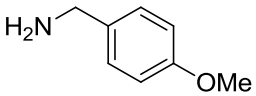
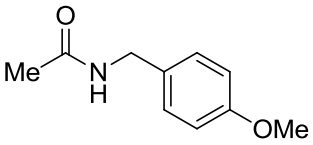
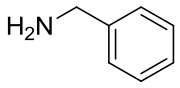
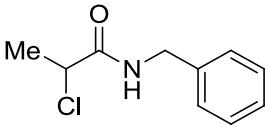
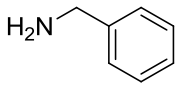
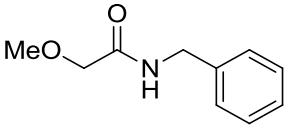
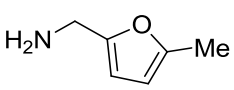
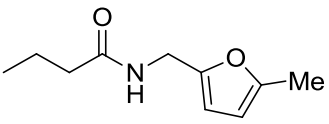
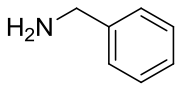
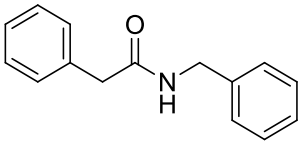
2.5 Substrate Scope

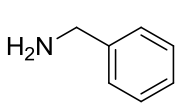
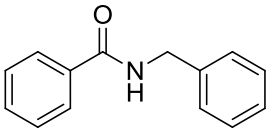
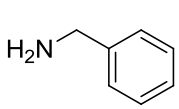
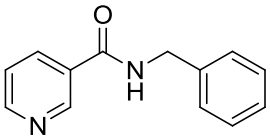
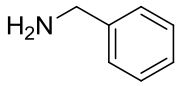
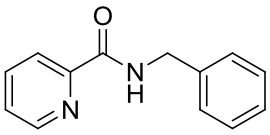
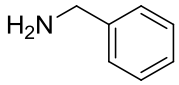
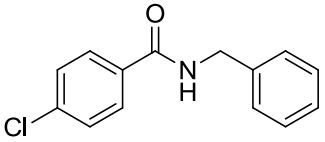
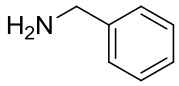
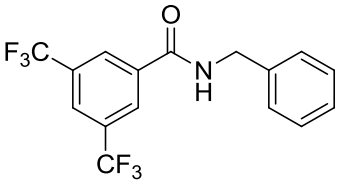
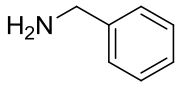
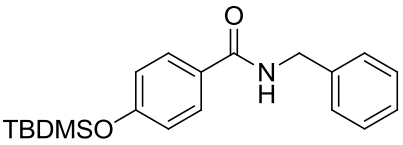
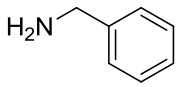
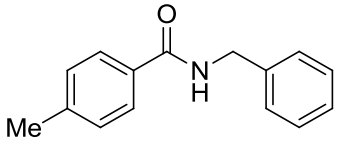
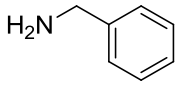
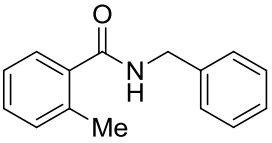
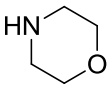
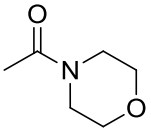
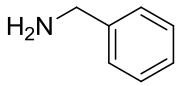
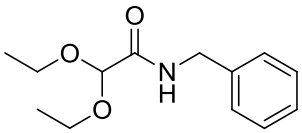
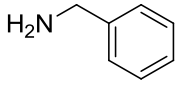
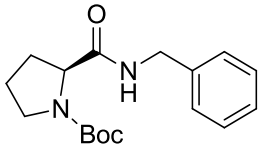
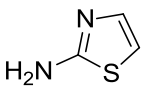
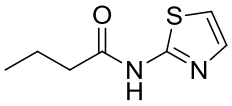
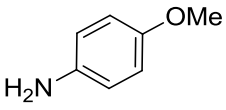
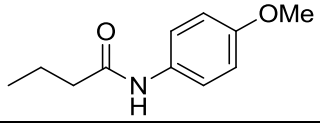
2.5.1 Amide and Amine Substrate Scope

Using the optimised reaction conditions, with Cp_2ZrCl_2 (5 mol%) as the catalyst and cyclohexane as the reaction solvent, the substrate scope of transamidation was explored (Table 7).

Table 7. Transamidation substrate scope[a]



Entry	Starting Amine	Amide Product		Time (h)	Temp (°C)	Yield[b] %
1			**2.03**	5	80	88 (100)
2			**2.06**	5	80	91 (100)
3			**2.07**	5	80	89 (100)
4			**2.08**	5	80	78 (100)[c]
5			**2.09**	5	80	81 (100)[c]
6			**2.10**	5	80	92 (100)
7			**2.11**	5	80	87 (96)
8			**2.12**	8	80	90 (100)
9			**2.13**	8	80	84 (96)

10			**2.14**	18	80	93 (100)
11			**2.15**	18	80	84 (100)
12			**2.16**	18	80	86 (100)
13			**2.17**	18	80	76 (89)
14			**2.18**	18	80	93 (100)
15			**2.19**	18	80	73 (81)
16			**2.20**	18	80	66 (72)
17			**2.21**	18	80	- (4)
18			**2.22**	18	80	86 (95)
19			**2.23**	18	80	84 (91)
20			**2.24**	24	80[d]	73 (87) > 99% *ee*
21			**2.25**	18	100[e]	68 (80)
22			**2.26**	18	100[e]	54 (81)

[a]Reactions performed on 3 mmol scale with 3.6 mmol of amine in 3.0 mL of solvent. [b]Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction carried out on 2 mmol scale with 2.4 mmol of amine in 2.0 mL of solvent. [d]Reaction carried out by Helen V. Lomax, amide (4 mmol), amine (4.8 mmol) in 4.0 mL of solvent. [e]Reaction carried out in *n*-heptane.

Primary aliphatic amines gave good yields of secondary amides in 5-8 hours at 80 ^{o}C when reacted with butyramide (Table 7, entries 1-3), acetamide (Table 7, entries 4 and 5) and 2-phenylacetamide (Table 7, entry 9). Pleasingly even at the elevated temperatures alkyl halides were tolerated within the reaction. (±)-2-Chloropropionamide underwent a clean reaction with benzylamine giving a high yield of the secondary amide product (Table 7, entry 6). Due to the highly non-polar nature of the cyclohexane solvent, an S_N2 reaction between the amine and alkyl chloride is disfavoured. A good functional group tolerance was also demonstrated including unsaturated bonds (Table 7, entry 2), protected phenols (Table 7, entry 5) as well as small heterocycles (Table 7, entry 8). Alkyl ethers, which have previously been seen to inhibit transamidation with group IV metals,[30] were well tolerated in the reaction giving a high yield of product (Table 7, entry 7). The presence of the alkyl ether in such close proximity to the amide could aid the binding of the catalyst. Features similar to this have literature precedence for aiding and increasing primary amide reactivity towards nucleophiles *via* coordination to the metal catalyst or promoter.[69,82]

A slightly longer reaction time of eight hours was required when 5-methylfurfurylamine was used (Table 7, entry 8). This could be due to weak Lewis basic interactions of the oxygen with the catalyst reducing catalytic activity. 2-Phenylacetamide also required a slightly longer reaction time to achieve a high yield of the secondary amide (Table 7, entry 9). Increased steric crowding around the amide carbonyl could explain the slower reaction due to reduced catalyst-amide interactions.

Longer reaction times were required for more chemically robust aromatic primary amides (Table 7, entries 10-16), which could be explained by the lower electrophilicity of the amide-carbonyl carbon as a result of increased conjugation with the aromatic system. However very good yields were obtained with benzamide (Table 7, entry 10) as well as pyridine based amides (Table 7, entries 11 and 12)

highlighting the tolerance of the catalytic system towards nitrogen based heterocycles. The close proximity of the nitrogen, in picolinamide and nicotinamide, to the primary amide could aid in reactivity as mentioned previously for 2-methoxyacetamide (Table 7, entry 7).

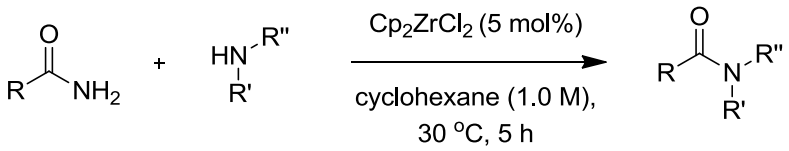
4-Chlorobenzamide (Table 7, entry 13) also gave a good yield of secondary amide although lower than pyridine or other aromatic amides (Table 7, entries 10-12). 3,5-Bis(trifluoromethyl)benzamide gave an excellent yield of secondary amide product, likely due to the highly electron withdrawing nature of the two trifluoromethyl groups (Table 7, entry 14). Sterically bulky silyl-ethers were also shown to remain intact through the reaction (Table 7, entry 15) with only protected product and starting materials seen after the reaction. Interestingly on comparison of the reactivity of 2- and 4-methyl benzamide, the presence of the methyl group in the 2-position inhibited the catalytic activity, with minimal conversion into product seen (Table 7, entry 17). Steric interactions with the catalyst that prevent binding, could explain the lack of reactivity.

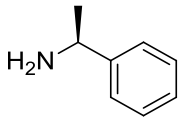
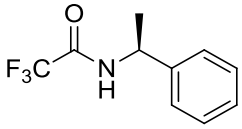
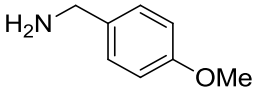
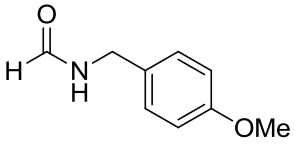
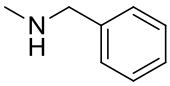
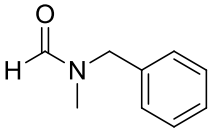
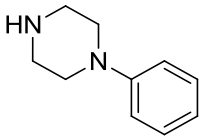
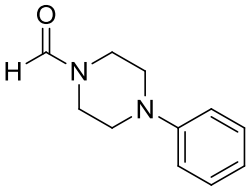
More sterically demanding substrates also required longer reaction times to achieve moderate to excellent yields of products. Morpholine reacted with acetamide to give the tertiary amide but even after 18 hours still did not go to completion (Table 7, entry 18). 2,2-Diethoxyacetamide (Table 7, entry 19) and *N*-Boc-L-prolinamide (Table 7, entry 20) both of which are doubly substituted at the α-position, also required longer times to achieve reasonable yields of secondary amide products. The double substitution present on these amides could have increased steric interactions with either the nucleophile or catalyst, so lowering reactivity. However both the Boc protecting group and *ee* were maintained throughout the reaction. The *ee* was confirmed as >99% by HPLC by comparison with the opposite enantiomer of pure product.

Two anilinic nucleophiles, 2-aminothiazole (Table 7, entry 21) and 4-methoxyaniline (Table 7, entry 22), required an elevated temperature of 100 °C with *n*-heptane as the solvent to accommodate for the increased temperature. As well as this a longer reaction time of 18 hours was required, giving reasonable conversions and yields of products. This was most likely due to the reduced nucleophilicity of the amine, due to conjugation of the nitrogen lone-pair with the attached aromatic ring.

2.5.2 Transamidation of Favourable Substrates

Table 8. Low temperature transamidation scope



Entry	Starting Amine	Product Amide		Yield %
1			**2.26**	- (27)[c,d] 88[c] (100)
2			**2.27**	90 (100)
3			**2.28**	95 (100)
4			**2.29**	89 (100)

[a]Reactions performed on 3 mmol scale with 3.6 mmol of amine in 3.0 mL of solvent. [b]Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra. [c]Determined by ^{1}H NMR analysis using 2,5-dimethylfuran as an internal standard. [d]No catalyst present.

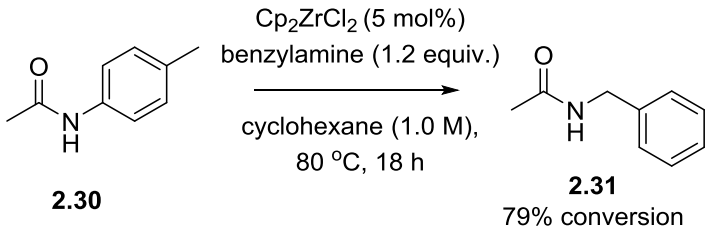
Favourable substrates such as formamide and 2,2,2-trifluoroacetamide underwent transamidation at only 30 °C. The reactive nature of these amides allowed transamidation under mild conditions as the amide carbonyl-carbon is very electrophilic in both cases. 2,2,2-Trifluoroacetamide has three electronegative fluorines at the α-position, significantly reducing the electron density at the amide carbonyl-carbon and so increasing reactivity towards nucleophiles. The transamidation of 2,2,2-trifluoroacetamide with (*S*)-α-methylbenzylamine yielded 88% of secondary amide product in five hours under very mild conditions (Table 8, entry 1). The *ee* of the amine was also maintained during the reaction, showing >99% *ee* by HPLC by comparison with a sample of the racemic product. Even with the

inherent reactivity only 27% conversion into products was found with no catalyst present under the same conditions (Table 8, entry 1).

The reactivity of formamides can also be rationalised on both electronic and steric grounds, in comparison with acetamide, in the same way aldehyde over ketone reactivity is rationalised. The weak electron donation of the methyl into the amide carbonyl is not present in formamide and neither is the steric factor brought about by the methyl. Formamide reacted cleanly with primary amines (Table 8, entry 2) as well as with acyclic (Table 8, entry 3) and cyclic secondary amines (Table 8, entry 4) to give excellent yields of substituted formamides, which find use as isonitrile precursors.[83] The *N*-arylamine group present in the piperazine showed no effect on catalytic activity, giving the tertiary formamide product in an 89% yield (Table 8, entry 4).

2.5.3 Secondary and Tertiary Amides

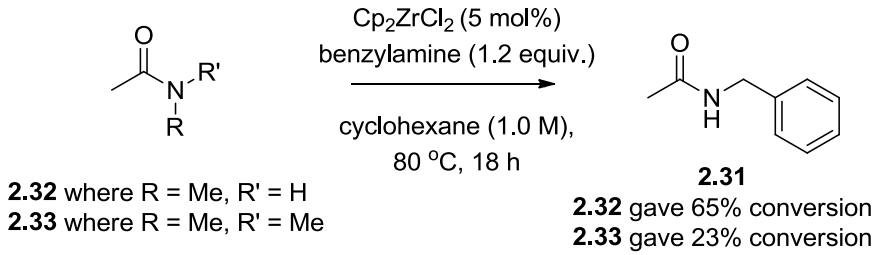
The transamidation of secondary alkyl and aryl amides has been shown to be catalysed by Lewis acid metal catalysts (*vide supra*).[30] It was investigated as to whether the catalytic system was active in a system in which a thermodynamic driving force would be present. 4'-Methylacetanilide **2.30** was transamidated under the optimised reaction conditions to give **2.31** in 79% conversion (Scheme 41). The resonance stabilised 4-methylaniline leaving group provides an effective driving force for the reaction. However even after 18 hours only 79% conversion was achieved highlighting the lower reactivity of secondary amides in the catalytic system.



Scheme 41. Transamidation of 4'-methylacetanilide with benzylamine

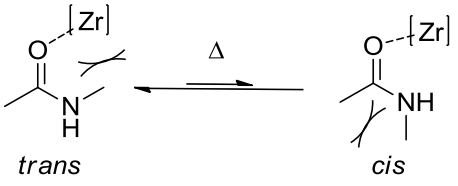
The transamidation of *N*-methylacetamide **2.32** and *N*,*N*-dimethylacetamide (DMAC) **2.33** with benzylamine was investigated to compare the relative reactivities of secondary and tertiary amides to primary amides. In each case the amide leaving group, methylamine or dimethylamine (boiling points of -6 °C and 7 °C

respectively), will be a volatile product so providing a thermodynamic driving force for the reaction. However a secondary or tertiary amide may bind or interact with the catalyst differently due to either steric or electronic differences. It was seen that even after 18 hours *N*-methylacetamide **2.32** and DMAC **2.33** achieved 65% and 23% conversion into *N*-benzylacetamide **2.31** respectively (Scheme 42). This further highlighted the lower reactivity of secondary and tertiary amides under the reaction conditions, as well as the selectivity towards primary amides. As seen previously acetamide achieved 100% conversion into *N*-benzylacetamides (Table 7, entry 5).



Scheme 42. Transamidation of *N*-methylacetamide and DMAC with benzylamine

The lower conversion, seen especially with the tertiary amide **2.33**, indicates the sensitivity to steric effects in the substrate-catalyst interactions. The secondary amide **2.32** would likely have the ability, especially at the elevated temperatures of the reaction, to overcome the barrier of rotation around the amide C-N bond and adopt the normally unfavourable *cis* conformer,[84] so minimising any steric interactions with the co-ordinating catalyst (Scheme 43). Further steric interactions would be seen with tertiary amide **2.33** leading to the observed lower conversion into product.

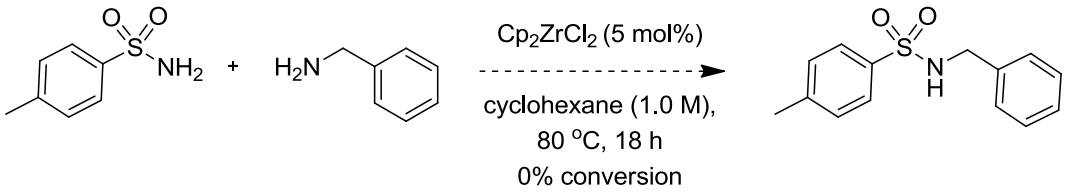


Scheme 43. *Cis* and *trans N*-methylacetamide 2.32 isomers

2.5.4 Phosphinamides and Sulfonamides

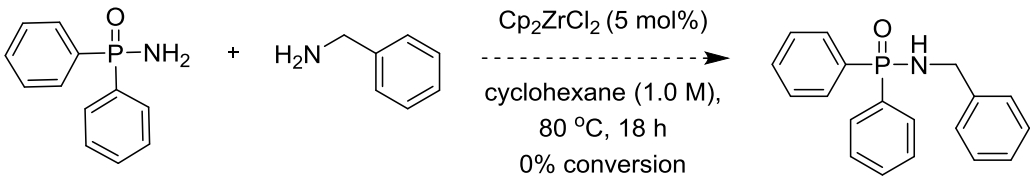
Although the reaction of sulfonamides with amines, which would be termed trans-sulfonamidation, has been reported in the literature it requires prolonged heating at very high temperatures (200 °C).[85] It was investigated as to whether Cp_2ZrCl_2 would

be an effective catalyst for the reaction of a sulfonamide with an amine (Scheme 44). Using the optimised reaction conditions *p*-toluenesulfonamide was reacted with benzylamine, however no reaction was observed after 18 hours.



Scheme 44. Reaction of *p*-toluenesulfonamide with benzylamine using a Cp_2ZrCl_2 catalyst

The reaction of phosphinamides with amines, which would be termed trans-phosphinamidation, has no literature precedence. As such developing a methodology to perform this reaction would provide an interesting route towards substituted phosphinamides. However on reaction of diphenylphosphinamide with benzylamine, under the previously optimised reaction conditions with Cp_2ZrCl_2 present, no reaction was observed after 18 hours (Scheme 45).



Scheme 45. Reaction of diphenylphosphinamide with benzylamine using a Cp_2ZrCl_2 catalyst

2.5.5 Reaction Limitations

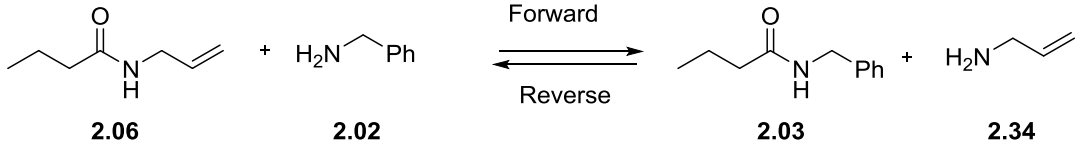
During the investigations around the substrate scope of the reaction it was noted that some substrates were not tolerated within the reaction. Use of substrates containing hydroxyl groups, such as the hydroxy amide (*S*)-lactamide, showed little to no reactivity in the reaction system. Due to zirconium's oxophilicity it is possible that strong binding between the hydroxyl group and the catalyst was causing inhibition of activity. As well as this more chemically robust substrates such as pivalamide or sterically hindered substrates such as *t*$BuNH_2$ showed <10% conversion even after prolonged reaction times.

2.6 Mechanistic Investigations

2.6.1 Reversibility Studies

Transamidation has been used previously for the thermally neutral interchange of secondary amides with primary amines. It has been seen that with certain catalysts a point of equilibrium could be reached.[30] To see if the developed catalytic system was active for this process two similarly reactive yet spectroscopically identifiable substrates were chosen. *N*-Benzyl butyramide **2.03** and *N*-allylbutyramide **2.06** (Table 9) were reacted separately with the corresponding primary amines **2.02** and **2.34**

Table 9. Reversibility studies[a]



2.06 **2.02** **2.03** **2.34**

Amide Ratio (2.06 / 2.03)[b]	
Forward	Reverse
92/8	3/97

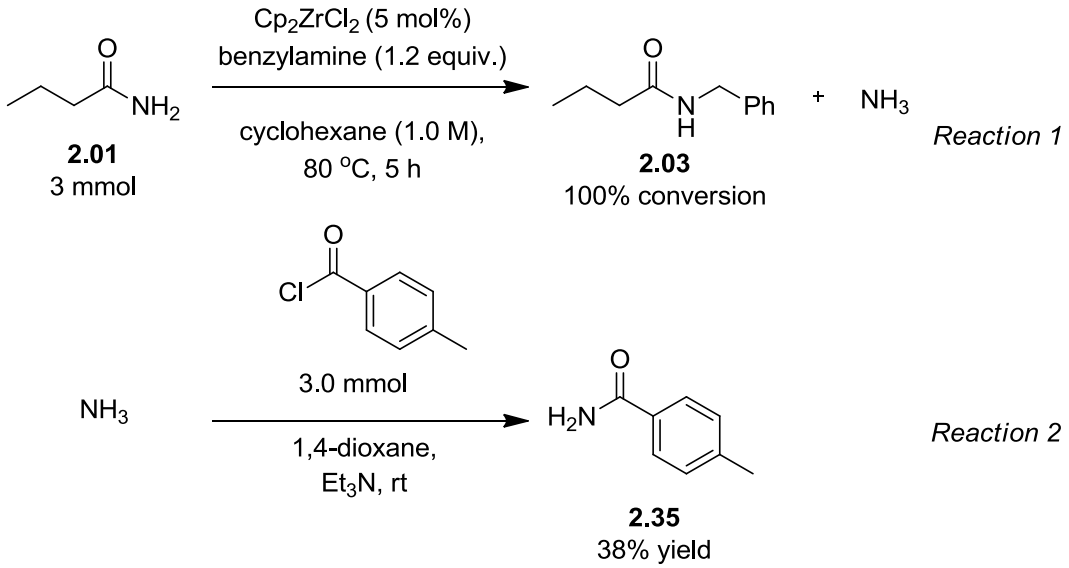
[a]Amide (1 mmol), amine (1 mmol), Cp_2ZrCl_2 (5 mol%), cyclohexane (1.0 M), 80 °C, 18 h. [b] Conversion determined by analysis of the crude ^{1}H NMR spectra.

On analysis of the product distribution after 18 hours little transamidation of starting amides **2.06** and **2.03** was seen (Table 9). The low reversibility of this reaction showed the synthetic merit of being able to drive the reaction towards the desired substituted product when ammonia is used as the leaving group as in primary amides.

2.6.2 Ammonia Trapping

In the transamidation of primary amides the nitrogen of the substituted amide product was shown, by James W. Walton, to come from an attacking amine nucleophile, with the loss of ^{15}N from an enriched benzamide compound. To identify and confirm that the primary amide nitrogen is lost as ammonia gas, an experiment was carried out to trap or incorporate the ammonia into an isolatable compound. In tandem to the parent reaction, between butyramide **2.01** and benzylamine **2.02** (Scheme 46**.** *Reaction 1*), a

cannula leading into a reaction vessel containing *p*-tolyl chloride (Scheme 46**,** *Reaction 2*) was setup. The ammonia given off would react to produce *p*-toluamide **2.35** showing that ammonia gas is released from the reaction.



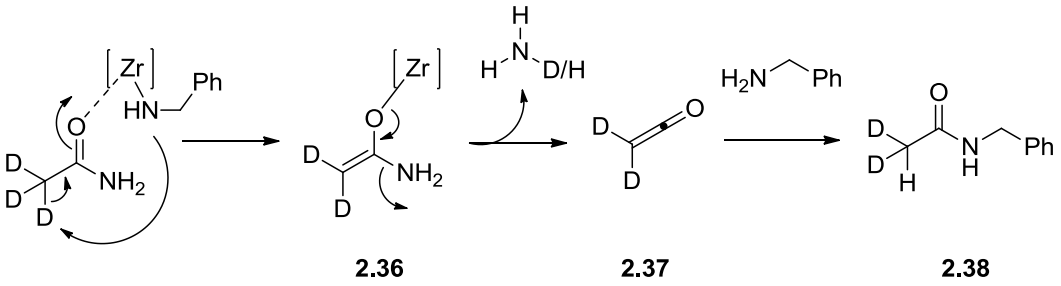
Scheme 46. Ammonia trapping experiment

The formed ammonia gas was passed from *Reaction 1* (Scheme 46) *via* cannula, into *Reaction 2* (Scheme 46) and gave *p*-toluamide **2.35** in 38% yield. The low yield could be explained by the possible loss of ammonia gas through leakage in the cannula setup. Additionally only one equivalent of ammonia will be produced theoretically during the reaction and procedures synthesising amides from ammonia gas and an acid chloride have an excess of the gas present.[86] However the isolated primary amide confirmed the loss of ammonia from the transamidation reaction as ammonia gas.

2.6.3 Labelling Studies

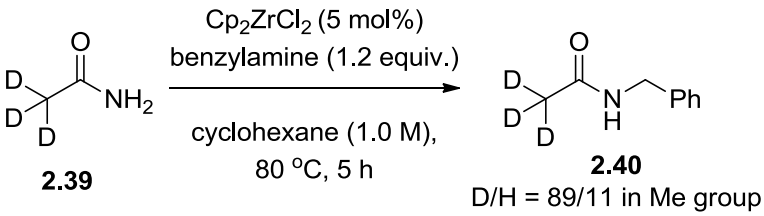
Cp_2ZrCl_2, in combination with a base, is known to form enolates with amides which can then be used in aldol reactions.[87] In our case a bound Zr-amido ligand could act to deprotonate the α-methyl so forming a zirconium enolate **2.36** (Scheme 47). Subsequently an elimination-addition pathway could occur to produce the desired transamidated product *via* a ketene **2.37**. In order to investigate whether this pathway was possible an α-deuterium labelled amide was synthesised. If enolisation was taking place, with subsequent elimination of ammonia, then addition of the amine

across the ketene **2.37** would produce a 2,2-deuterio-2-hydrido secondary amide **2.38** product.



Scheme 47. Possible elimination-addition pathway

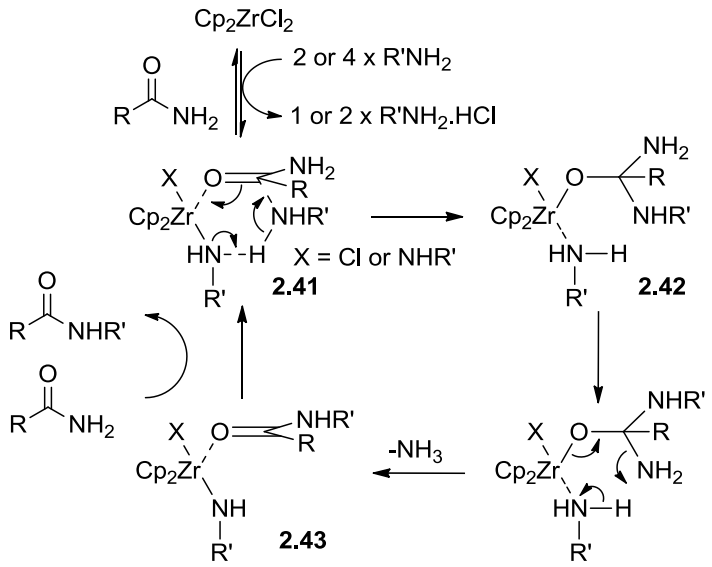
Synthesis of 2,2,2-trideuterioacetamide **2.39** was carried out using a modified literature method *via* hydration of d3-MeCN.[88] On reaction of 2,2,2-trideuterioacetamide **2.39** with benzylamine (Scheme 48) the hydrogen incorporation at the α-position to the amide was calculated based on the ^{1}H NMR spectra of the purified product **2.40**. It showed that a D/H = 89/11 was present at the α-position. A solely ketene based mechanism would be expected to produce a D/H ≈ 67/33. The found ratio indicates that although an elimination-addition pathway cannot be ruled out for this substrate, it is likely that it is not part of the major reaction pathway. Furthermore benzamide (Table 7, entry 9), 2,2,2-trifluoroacetamide (Table 8, entry 1) and formamide (Table 8, entries 2-4) were successfully transamidated despite the lack of α-protons. As well as this the lower the pK_a of α-amide protons, the more labile they are to base, so enolisation and subsequent ketene formation would be easier. However 2-phenylacetamide (Table 7, Entry 8), that would have slightly more acidic α-protons, achieved 86% yield of *N*-benzyl product in eight hours. Comparing this with the 88% yield obtained for butyramide (Table 7, entry 1) in five hours, further reduces the likelihood that the reaction proceeded *via* an elimination-addition pathway.



Scheme 48. Transamidation of 2,2,2-deuterioacetamide

2.6.4 Proposed Mechanism

Investigations into the mechanism of the catalytic process were carried out by James W. Walton in parallel to the investigation of the synthetic scope. HPLC monitoring of the reaction between benzamide and benzylamine determined the rate order with respect to each reactant. It was found that the reaction was first order with respect to both the benzamide and Cp_2ZrCl_2 catalyst, upon submitting the data to kinetic analysis. However it was seen that the reaction was second order with respect to the benzylamine, with the amine likely acting as a base upon release of HCl from ligand exchange of a chloride with another molecule of benzylamine. Interestingly the rate order when a tertiary amine base such as *N*,*N*-diisopropylethylamine (DIPEA) was added to the reaction at varying concentrations, was shown to be zero order. In line with the kinetic data obtained a reaction mechanism was proposed as follows (Scheme 49); a zirconium amide (Zr-NHR) **2.41** is formed upon ligand exchange of chlorine for an amine, producing HCl which precipitates out of the reaction mixture as benzylamine hydrochloride. Complexation of the carboxamide to this zirconium-amide followed by addition of the amine to the carboxamide to give a tetrahedral intermediate **2.42**. If the addition is aided by the zirconium amide (Zr-NHR) then this could rationalise the second order rate with respect to amine seen in the reaction. Further to this the thermodynamically favourable loss of ammonia would generate the coordinated carboxamide product **2.43**. Ligand exchange of carboxamide could then allow the catalytic cycle to begin again.



Scheme 49. Proposed mechanism for the Cp_2ZrCl_2 catalysed transamidation

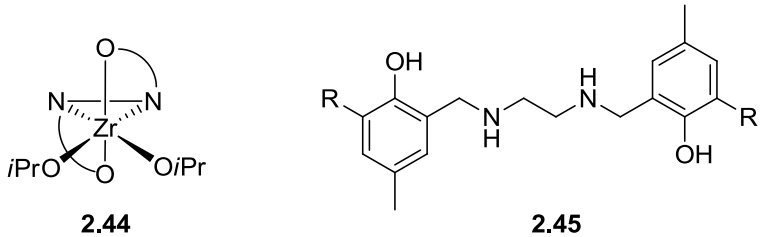
2.7 Further Work

Further work to the developed catalytic system was based around improving catalytic activity, so lower temperatures and catalyst loadings can be used for un-activated substrates. Using the insight gained into the mechanism by the kinetic work carried out (*vide supra*) and based around the proposed mechanism of the reaction, using tailored ligand systems could provide an improvement in catalytic efficiency.

Preformed Polymerisation Catalysts

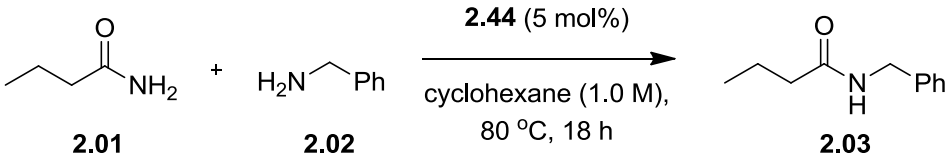
Work within our own department has been carried using preformed group 4 metal-ligand complexes for the synthesis of biodegradable polylactide polymers from *rac*-lactide.[89] The polymerisation is believed to proceed with a metal bound isopropoxide initiator attacking the carbonyl ester of the metal coordinated lactide.[90] The eventual loss of the new metal bound alkoxide from the ester allows the ring opening process to occur so giving a transesterified product. The process has similar groundings to the transamidation process and uses the same group 4 metals. If the isopropoxide was substituted for an amine, the transamidated product could possibly be formed. Group 4 bis(amino-phenolate) catalysts **2.44** (Figure 5) have been used for this process and could be catalytically active for transamidation reactions. Limited initial

results using the preformed zirconium-ligand species under the previously optimised conditions for transamidation were carried out (**Table 10**).



2.44 **2.45**

Figure 5. Preformed zirconium bis(amino-phenolate) catalysts and free ligand



2.01 **2.02** **2.03**

Table 10. Transamidation using preformed zirconium bis(amino-phenolate) catalysts[a]

Entry	Ligand 2.44 -R group	Conversion into 2.03[b]
1	*t*Bu	33
2	Me	5

[a]Reactions performed on 1 mmol scale with 1.2 mmol of amine in 1.0 mL of solvent. [b]Conversion determined by analysis of the crude ^{1}H NMR spectra.

The results showed lower catalytic activities than Cp_2ZrCl_2, however a difference between the *t*Bu (Table 10, entry 1) and Me (Table 10, entry 2) was seen, possibly due to greater solubility afforded by the *t*Bu groups. The catalysts used contained isopropoxide ligands, so it is possible that the isopropoxide ligands were not displaced by the attacking amine. Replacing the isopropoxide ligands with more labile chlorides could allow better ligand displacement and so possibly enhance any catalytic activity.

2.8 Conclusions

A catalytic system for the transamidation of primary amides with amines has been developed and optimised. By using commercially available Cp_2ZrCl_2, which was identified by a screen of various metal catalysts, the methodology has been applied to

a range of different functional group containing primary amides and amine, the products of which were obtained in moderate to excellent isolated yields. The reaction employed lower temperatures than previous examples for this non-reversible process as well as a low catalyst loading. For favourable substrates such as formamide or 2,2,2-trifluoroacetamide lower temperatures of 30 °C are sufficient to obtain excellent chemical yields.

It was found that primary amides showed much greater reactivity over both secondary and tertiary alkylamides. As well as this, low reactivity was seen on addition of an amine to the formed amide product further highlighting the selectivity of the reaction from primary amide into secondary or tertiary amide product. Gaseous ammonia was proven to be produced from the reaction *via* secondary trapping with an acid chloride.

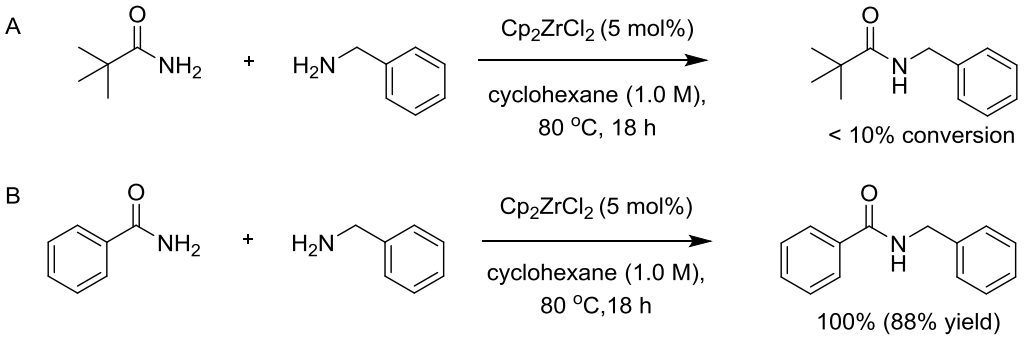
A mechanism was eluded to based on monitoring and analysis of the reaction by James W. Walton. This found that the reaction was first order with respect to all components except the amine which was shown to be second order. Also through the use of deuterium labelled substrates an enolisation-ketene mechanism has been shown to not be the major pathway of the reaction.

Chapter 3 – Development of an Enhanced Transamidation Methodology using Zirconocene Dichloride

Chapter 3: Results and Discussion II

3.1 Aims

The aim of this work was to investigate and develop an improved transamidation methodology based on our original zirconocene dichloride catalysed work (Chapter 2). A more catalytically active methodology could also allow more chemically robust substrates to be transamidated efficiently (Scheme 50, A) or undergo a quicker rate of reaction than had been seen previously (Scheme 50, B).

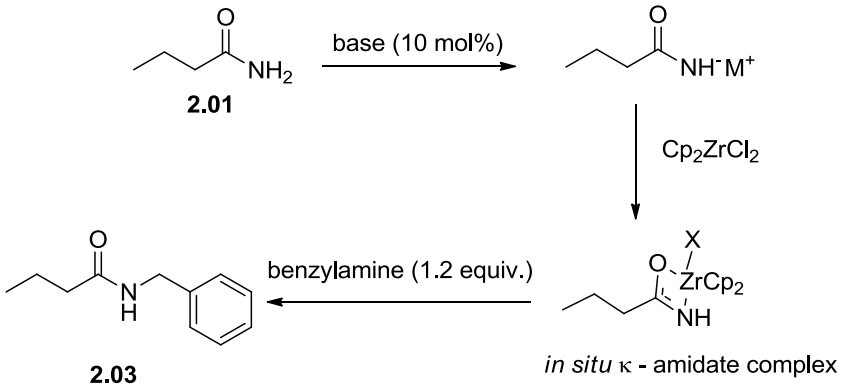


Scheme 50. Highlighted substrate limitations using Cp_2ZrCl_2 methodology of A) robust substrates and B) non-favourable substrates

3.2 Initial Work

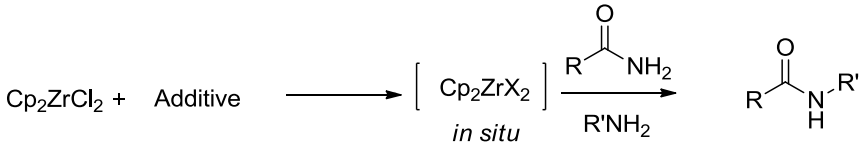
Two different approaches were initially taken towards developing a more catalytically active transamidation methodology.

The first approach used a catalytic amount of a strong base to deprotonate the primary amide, thus forming a metal carboxamide species. Following this, introduction of Cp_2ZrCl_2 could form a κ-amidate complex. κ-Amidate species are known to be active species in the catalytic cycle with other transition metal catalysed transamidations.[91] Although the base is only being added in a catalytic amount, initial formation of this complex could lead to an increased overall reaction rate. Addition of the amine would then lead to the transamidated product (Scheme 51).



Scheme 51. Use of a catalytic amount of a strong base to form a κ-amidate complex *in situ*

A second approach focussed on forming a more active catalytic species. This could be achieved by exchange of the chlorides on the zirconocene for less Lewis basic and so more labile ligands (Scheme 52). Subsequent addition of both the amide and amine could then lead to the transamidated product.

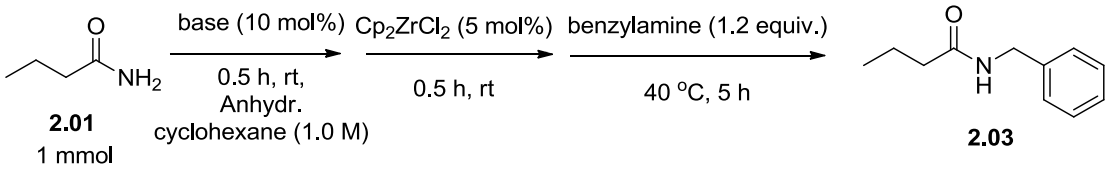


Scheme 52. *In situ* formation of a more active catalytic species

3.2.1 Use of Base for Enhanced Transamidation

Only bases with a pK_a >15, pK_a of the primary amide, were chosen in order to allow the formation of a metal-carboxamide species.

Table 11. Base screen



Entry	Base	Conversion into 2.03 (%)[a]
1	-	4
2	$NaNH_2$	4
3	*n*BuLi (2.5 M in Hex)	0
4	NaH (60% in mineral oil)	0
5	NaO*t*Bu	0
6	LiHMDS (1.0 M in THF)	0
7	LiHMDS (1.0 M in PhMe)	0
8	NaHMDS (1.0 M in THF)	0

[a]Conversions were determined by analysis of the crude ^{1}H NMR spectra.

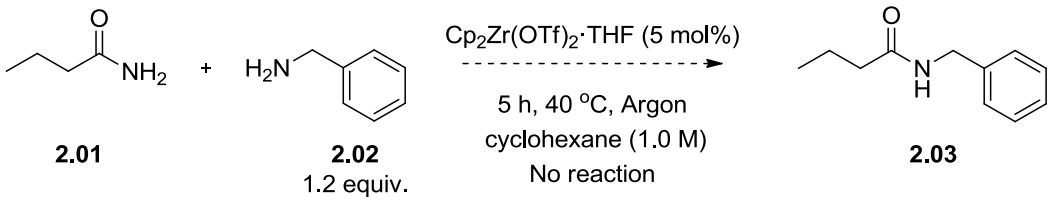
It was seen that when the reaction was run at 40 °C only 4% conversion was observed (Table 11, entry 1). These conditions were chosen and used throughout these investigations, as they indicated the reaction proceeded but at a significantly reduced rate. Subsequently any increase in conversion would be due to changes made to the reaction. In order to maintain consistent concentrations between reactions, cyclohexane was used to make all reactions 1.0 M when a solution of base was used.

Analysis of the ^{1}H NMR spectra indicated that in nearly all of the reactions all starting materials were returned, showing that use of the base somehow inhibited catalytic activity. In all cases catalyst degradation could have occurred as even background rates of reaction (Table 11, entry 1) were not observed (Table 11, entries 3-8). Only $NaNH_2$ showed any conversion into product with 4% (Table 11, entry 2), however this was only comparable to the background rate of the reaction.

Based on these results the use of catalytic amounts of base to achieve a more active catalytic system was abandoned.

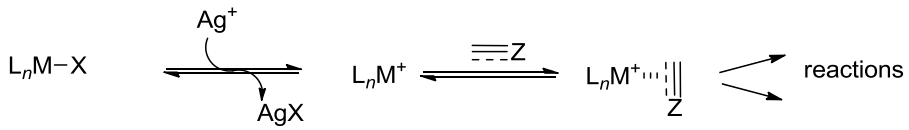
3.2.2 Use of Low Lewis Basicity Ligands for Enhanced Transamidation

As mentioned previously, a catalytic species containing labile, low Lewis basicity ligands could be more catalytically active for the transamidation of amides with amines. Initially a commercially available zirconocene complex, zirconocene bis(triflate) THF adduct (Cp_2ZrOTf_2·THF), was used as a catalyst in the parent reaction (Scheme 53). Interestingly no reaction was observed at 40 °C even though the catalytic species already contains the labile ligands. An explanation could be due to the presence of THF within the complex which would occupy the normally vacant orbital, in Cp_2ZrCl_2, thus creating an 18 electron complex. This could prevent the necessary catalyst-substrate interactions from occurring, so an alternative approach was undertaken to form the complex *in situ.*



Scheme 53. Zirconocene bis(triflate) catalysed transamidation

Silver salts have precedence for irreversible halide abstraction driven by the precipitation of the highly insoluble silver chloride (AgCl) as well as the particularly high halophilicity of silver. It has often been used for the activation of organic molecules, organometallics as well as metal complexes (Scheme 54). In metal complexes the halide abstraction is often necessary for the generation of an unsaturated coordination sphere.[92]

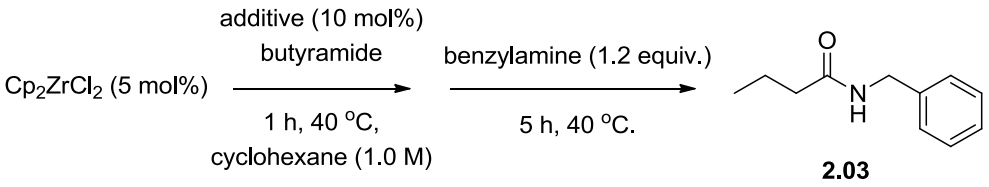


Scheme 54. Silver promoted halide abstraction in metal complexes

It was reasoned that by using silver salts of low Lewis basic anions, chloride abstraction could be achieved from the Cp_2ZrCl_2 to give a new and potentially more active zirconocene species. In order to quantify the coordination ability of the new ligand a key reference was used.[93] The authors analysed >520,000 metal complexes from the Cambridge Structural Database (CSD). Using this, the anions were

quantified and ranked by the percentage of complexes where coordination to the transition metal was observed in the crystal structure and subsequently given a coordination ability index (a^{TM}). This was used as a guide as to which ligands would be used for the formation of a more active catalyst.

Table 12. Metal salts of lower a^{TM} than chloride or low Lewis basicity

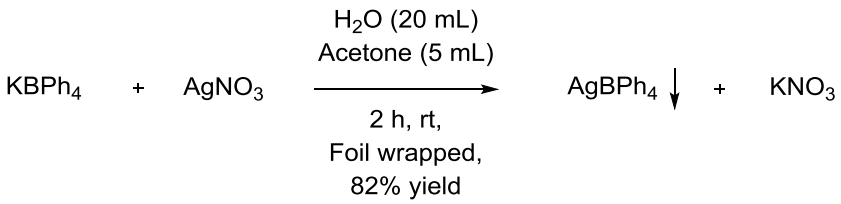


2.03

Entry	Silver Salt	Coordination ability index of anion[93] (a^{TM})	Conversion into 2.03 (%)[a]
1	-	1.3 (Chloride)	4
2	AgI	0.9	11
3	AgOMs	0.5	37
4	$AgN(SO_2CF_3)_2$	-	30
5	AgOTf	-0.4	43 (0[b])
6	KOTf	-0.4	23
7	$AgClO_4$	-0.6	15
8	$AgPF_6$	-1.6	<1
9	$AgBPh_4$	-1.8	32

[a]Conversions were determined by analysis of the crude ^{1}H NMR spectra.
[b]Without Cp_2ZrCl_2

Only commercially available silver salts were used for ease of screening, with the exception of silver tetraphenylborate ($AgBPh_4$) which was synthesised using literature methods.[94]



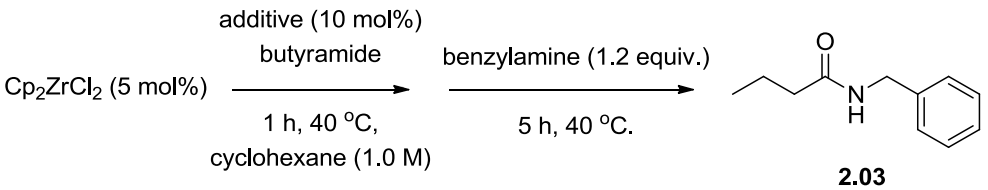
Scheme 55. Synthesis of silver tetraphenylborate ($AgBPh_4$)

Interestingly the use of silver salts with a lower a^{TM} than chloride gave both increases and decreases in conversion with no discernible trend in activity. Silver hexafluorophosphate ($AgPF_6$) was shown to inhibit catalytic activity completely

(Table 12, entry 7). This could be as a result of the formation of an inactive zirconocene difluoride species, which has literature precedence for forming when zirconocene complexes are reacted with PF_6 salts.[95] A small increase was seen with both silver iodide (AgI) and silver perchlorate ($AgClO_4$) (Table 12, entries 2 and 6 respectively) from the background rate of reaction (Table 12, entry 1). A further increase in catalytic activity was seen with silver mesylate (AgOMs) and silver tetraphenylborate ($AgBPh_4$) (Table 12, entries 3 and 9 respectively). Commercially available silver triflimide ($AgN(SO_2CF_3)_2$) was also shown to increase conversion to 30% (Table 12, entry 4). Although not classified within the original paper the coordination ability of triflimide was assumed to be low, based on the available pK_a data in comparison with triflate.[96] The greatest increase in activity was observed with silver triflate (AgOTf) (Table 12, entry 5) which showed a 43% conversion into product. To compare reactivity and identify that the silver salt was key for the increase in catalytic activity, potassium triflate (KOTf) was used as a catalytic additive. Interestingly, although an increase in conversion to 23% was observed (Table 12, entry 6) the increase was not as high as that observed with AgOTf (Table 12, entry 5). This showed that our initial aim, to use the halophilicity of silver to drive the formation of a more active catalyst, was effective.

Subsequent to this, it was reasoned that anions of a higher a^{TM} than chloride would be inactive in the system due to strong ligand-metal interactions causing catalyst inhibition. Readily available silver salts of three anions with higher a^{TM} than chloride were examined in the reaction (Table 13).

Table 13. Silver salts of higher a^{TM} than chloride



2.03

Entry	Silver Salt	Coordinating ability index of anion[93] (a^{TM})	Conversion into 2.03 (%)[a]
1	-	1.3 (Chloride)	4
2	$Ag_3(PO_4)_4$	2.1	<1
3	$AgNO_2$	1.7	<1
4	AgSCN	1.6	50 (2[b])

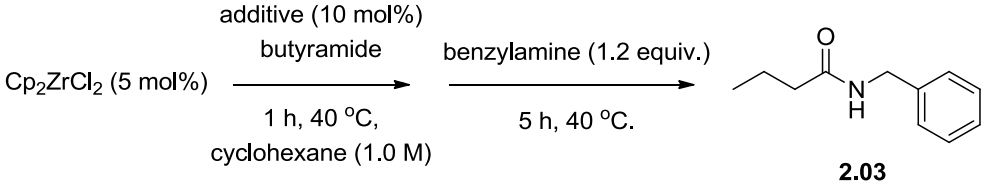
[a] Conversions were determined by analysis of the crude ^{1}H NMR spectra.
[b] Without Cp_2ZrCl_2

It was seen that with two of the three silver salts used, silver phosphate ($AgPO_4$) and silver nitrite ($AgNO_2$) (Table 13, entries 2 and 3 respectively), completely inhibited any catalytic activity. This would be predicted as both PO_4^{3-} and NO_2^- have a^{TM} values above that of chloride. However silver thiocyanate (AgSCN) (Table 13, entry 4) showed a significant increase, not only over the background rate of reaction (Table 13, entry 1) but over AgOTf (Table 12, entry 5). Only 2% conversion was observed carrying out the same reaction without using Cp_2ZrCl_2 (Table 13, entry 4**)**, indicating that both are needed in combination to achieve the desired increase in conversion.

3.2.3 Use of Thiocyanate and Isothiocyanate Ligands for Enhanced Transamidation

Further to this result, other thiocyanate and isothiocyanate sources were investigated as to whether they could further increase the reactivity of the Cp_2ZrCl_2.

Table 14 Thiocyanate and isothiocyanates as catalytic additives



2.03

Entry	SCN/NCS source	Conversion into 2.03 (%)[a]
1	AgSCN	50(2[b])
2	KSCN	62(1[b])
3	NaSCN	58
4	NH_4SCN	78(5[b])
5	Bu_4NSCN	15
6	Me_3SiNCS	85(1[b])

[a]Conversions were determined by analysis of the crude ^1H NMR spectra.
[b]Without Cp_2ZrCl_2

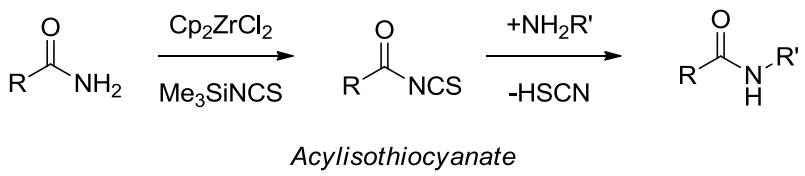
Interestingly it was found that contrary to previous results where the alkali metal salt of the ligand showed reduced conversion into products (Table 12, entry 6) a number of thiocyanate and isothiocyanate catalytic additives increased the conversion into product **2.03** further than AgSCN (Table 14, entry 1). Potassium and sodium salts of thiocyanate gave modest increases in conversion (Table 14, entries 2 and 3) with 62% and 58% conversion respectively. Ammonium thiocyanate (NH_4SCN)

increased conversion into product **2.03** yet further (Table 14, entry 4) with 78% conversion. Interestingly trimethysilyl isothiocyanate (Me_3SiNCS) gave the highest conversion into product (Table 14, entry 6) with 85% conversion. Use of a non-Lewis acidic source of thiocyanate (Table 14, entry 5), as the tetrabutylammonium salt, showed only a small increase from the background rate of the reaction (Table 13, entry 1) highlighting the crucial role and specificity of the thiocyanate source for reactivity. The solubility of Me_3SiNCS in the reaction solvent might have given rise to the higher reactivity, as the solubility could allow more effective production of the active catalyst.

3.3 Reaction Optimisation

Following on from this result, Me_3SiNCS was used in combination with Cp_2ZrCl_2, to develop a more active catalytic transamidation methodology. In order to increase the initial 85% conversion into product **2.03** (Table 14, entry 5) towards quantitative conversion, optimisation of the reaction conditions was undertaken.

Initially it was investigated as to how altering the amount of catalytic additive present in the reaction would affect the conversion into product **2.03**. A mechanism was proposed with isothiocyanate acting as a nucleophilic catalyst for the reaction, in combination with Cp_2ZrCl_2. The intermediate acylisothiocyanate could then react with the amine, in an analogous manner to an acid chloride, and form amide product (Scheme 56). Although the addition product is normally formed on reaction of a nucleophile with an acylisothiocyanate, there is literature precedence for an acyl substitution reaction occuring.[97,98]



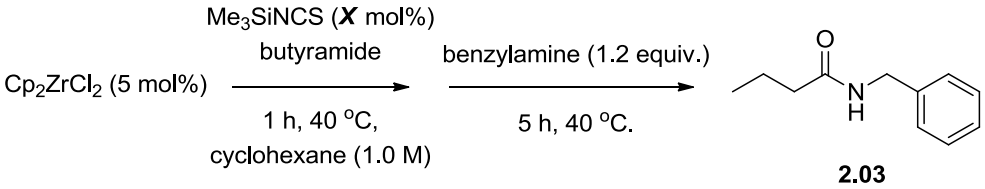
Scheme 56. A mechanism *via* an acylisothiocyanate

Acylisothiocyanates are often synthesised by the reaction of an acid chloride with an inorganic salt of thiocyanate i.e. KSCN or PbSCN.[99] An alternative method used on

an industrial scale to synthesise acylisothiocyanates, involves reacting Me_3SiNCS with an acid chloride with the formed Me_3SiCl subsequently distilled off.[99]

Based on this increasing the amount isothiocyanate could theoretically increase the rate of reaction, if the proposed nucleophilic catalysis mechanism was true, by producing a greater amount of acylisothiocyanate. Subsequent reaction with the amine *via* nucleophilic addition to the carbonyl would provide the amide product.

Table 15. Increased quantity of catalytic additive

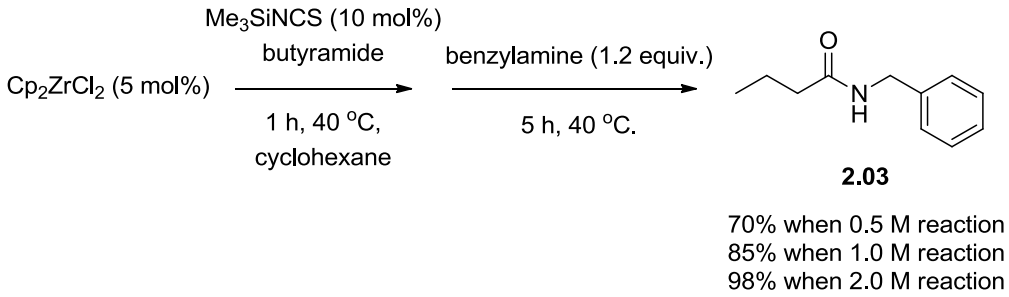


2.03

Entry	***X* mol% of Me_3SiNCS**	**Conversion into 2.03 (%)[a]**
1	10	85
2	20	70
3	50	30
4	100	23

[a]Conversions were determined by analysis of the crude ^1H NMR spectra.

It was seen that on increasing the amount of catalytic additive the conversion into product **2.03** was significantly reduced (Table 15, entries 2-4). Using 50 and 100 mol% of Me_3SiNCS (Table 15, entries 3 and 4) significant amounts of alternative product could be seen on analysis of the ^1H NMR spectra. This implied that a mechanism involving isothiocyanate as a nucleophilic catalyst could be ruled out, as a decrease in conversion was observed at increasing concentrations. If it was acting as a nucleophilic catalyst increasing the amount should theoretically have lead to a greater conversion into product.



Scheme 57. Effects of reaction concentration

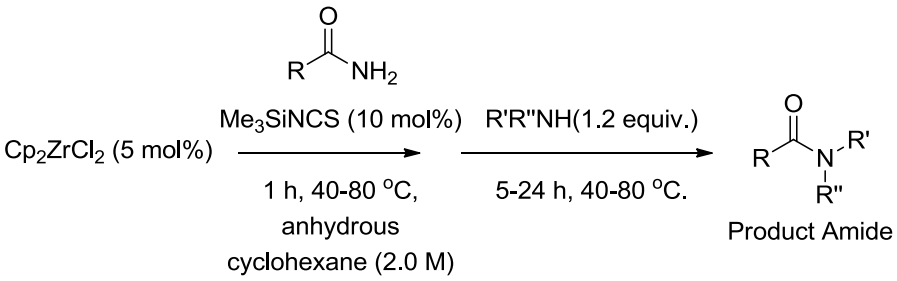
Subsequently it was investigated as to how changing the concentration of the reaction would affect the conversion into product **2.03** (Scheme 57). A further increase to 98% conversion was seen when the concentration of the reaction was increased to 2.0 M (Scheme 57). Lowering the concentration to 0.5 M decreased the conversion into product **2.03** to 70% (Scheme 57).

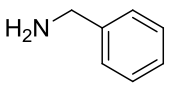
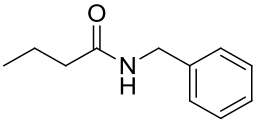
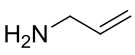
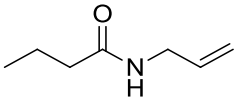
3.4 Substrate Scope

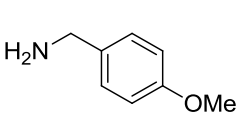
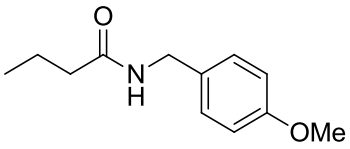
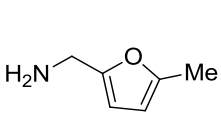
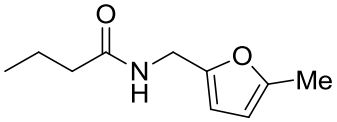
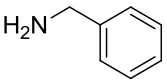
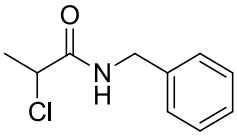
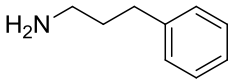
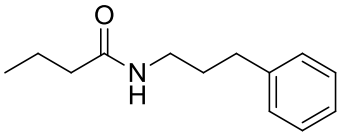
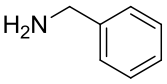
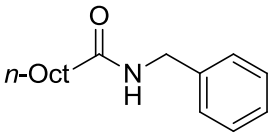
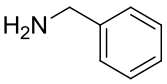
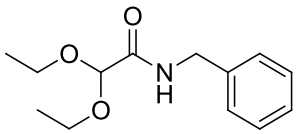
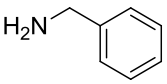
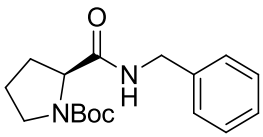
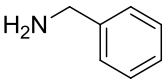
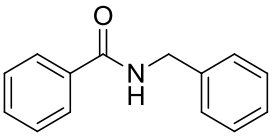
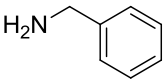
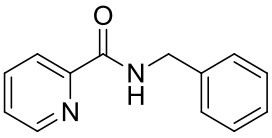
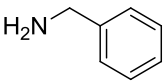
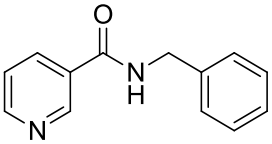
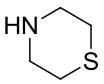
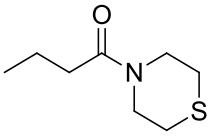
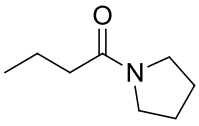
Using the optimised catalytic system the substrate scope of the reaction was explored.

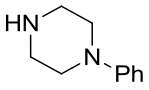
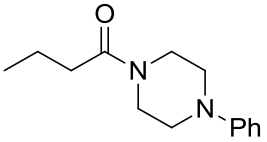
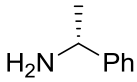
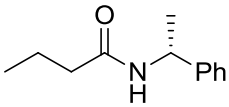
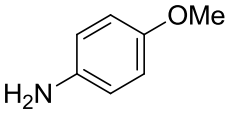
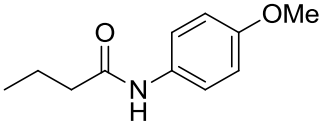
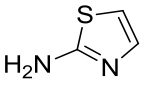
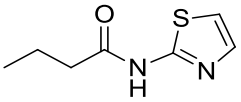
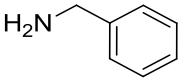
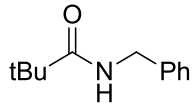
3.4.1 Scope of Amine and Amide Substrates

Table 16. Substrate scope using a combined Cp_2ZrCl_2 and Me_3SiNCS catalytic system[a]



Entry	Starting Amine	Product Amide		Time (h)	Temp (°C)	Yield (%)[b]
1			**2.03**	5	40	89 (98)
2			**2.06**	5	40	88 (97)

3			**3.01**	5	40	86 (98)
4			**2.12**	5	40	92 (98)
5			**2.10**	5	40	86 (92)
6			**3.02**	5	40	76 (85)
7			**3.03**	5	40	80 (93)[c]
8			**2.23**	18	40	90 (99)
9			**2.24**	24	40	82 (89)[c] >99% *ee*
10			**2.14**	18 5	40 80	- (55) 82 (96)
11			**2.16**	5	80	91 (99)
12			**2.15**	5	80	86 (99)
13			**3.04**	5	80	85 (90)
14			**3.05**	5	80	80 (86)

15			**3.06**	5	80	81 (88)
16			**3.07**	5	80	74 (84) >99% *ee*
17			**2.26**	24 5	40 80	- (0) 76 (82)
18			**2.25**	5	80	48 (52)
19			**3.08**	18	80	76 (82)

[a]Reactions performed on 3 mmol scale with 3.6 mmol of amine in 1.5 mL of solvent. [b]Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction carried out on 2 mmol scale with 2.4 mmol of amine in 1.0 mL of solvent.

The parent substrate was isolated in a good yield of 89% (Table 16, entry 1). The optimised catalytic system was shown to be tolerant of a wide variety of other functional groups. Allylamine produced a good 88% yield of the corresponding secondary amide product (Table 16, entry 2). Benzylic and similar amines including 4-methoxybenzylamine and 5-methylfurfurylamine reacted cleanly within the reaction system yielding 86% and 92% respectively of the corresponding secondary amides (Table 16, entries 3 and 4). Interestingly, unlike in the previously used reaction conditions (Chapter 2, Section 2.5.1), an extended reaction time was not required for 5-methylfurfurylamine. Alkyl halides were tolerated, with 2-chloropropionamide giving an 86% yield of amide from 92% conversion (Table 16, entry 5). A small amount of side product was noticed in the crude reaction, potentially from a S_N2 substitution of the chloride with an isothiocyanate anion. Aliphatic amines, such as 3-phenylpropylamine, were tolerated yielding a moderate 76% of the secondary amide product (Table 16, entry 6).

The scope of the primary amide was explored with *n*-nonamide yielding 80% amide product (Table 16, entry 7). Other amides required slight alterations to the reaction conditions with 2,2-diethoxyacetamide requiring 18 hours to give 90% yield (Table 16, entry 8), crucially the acetal functionality remained intact throughout the reaction. As discussed before (Chapter 2, Section 2.5.1) the lower reactivity

observed was likely due to steric crowding due to the substitution at the α-position. A prolonged reaction time of 24 hours was also required when a Boc protected amino acid derivative was used. However *N*-Boc-L-prolinamide did yield 82% of the transamidated product with the Boc group maintained throughout the reaction (Table 16, entry 9). >99% *ee* was maintained throughout the reaction as determined by HPLC by comparison with a pure sample of the D-product.

With more chemically robust amides such as benzamide, it was seen that at 40 °C only 55% conversion was achieved even after a prolonged reaction time of 18 hours (Table 16, entry 10). On increasing the temperature to 80 °C it was seen that an 82% yield of the secondary amide was formed in only five hours (Table 16, entry 10). Heterocycles including picolinamide and nicotinamide were well tolerated in the reaction giving high yields of 91% and 86% respectively (Table 16, entries 11 and 12). The presence of the pyridine nitrogen in close proximity to the amide, particularly with picolinamide, showed no effect on the reactivity in comparison with benzamide and may have aided in catalyst binding.

Cyclic secondary amines including thiomorpholine and pyrrolidine gave good yields of the tertiary amide products (Table 16, entries 13 and 14) but required the reaction to be conducted at 80 °C. The thioether present in thiomorpholine showed little effect on the reactivity giving 85% yield of tertiary amide (Table 16, entry 13). A slightly lower yield of 80% was produced when pyrrolidine was used (Table 16, entry 14). The presence of the tertiary amine in 4-phenylpiperizine was tolerated within the reaction yielding 81% of the tertiary amide product (Table 16, entry 15). Branched primary amines also required the use of elevated temperatures, likely due to increased steric bulk around the amino group. (*R*)-(+)-α-Methylbenzylamine gave the secondary amide product in a good isolated yield of 74%. The >99% *ee* of the starting materials was maintained through to the secondary amide product. This was determined by HPLC by comparison with the racemic product.

The use of anilinic amines required the reaction to be carried out at 80 °C due to the lower nucleophilicity. When 4-methoxyaniline was reacted at 40 °C no conversion into the secondary amide was seen (Table 16, entry 17). On increasing the reaction temperature to 80 °C, a 76% yield of the secondary amide was produced (Table 16, entry 17). Only a moderate yield of 48% of the secondary amide was formed when

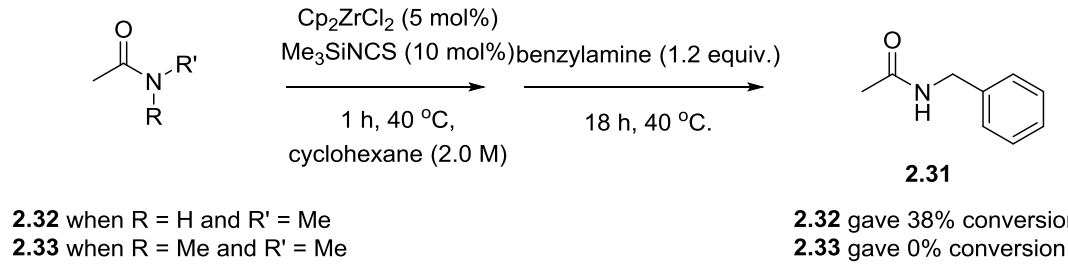
2-aminothiazole was reacted at 80 °C for five hours (Table 16, entry 18). Pleasingly, more robust substrates showed a significant increase in conversion when compared with the catalytic system without the Me_3SiNCS additive present. When pivalamide was reacted at 80 °C for 18 hours, a 76% yield of the secondary amide product was produced (Table 16, entry 19). Only 10% conversion was observed under the same reaction conditions without the catalytic additive present.

3.4.2 Reaction Limitations

Interestingly when both 2,2,2-trifluoroacetamide and formamide were subjected to the combined catalytic system, using Cp_2ZrCl_2 and Me_3SiNCS at 30 °C, little difference in reactivity was seen whether Me_3SiNCS was present or not. This is likely due to the highly reactive nature of these favourable substrates, such that use of the new, combined catalytic system does not increase the reactivity. As well as this similarly low activity was observed with or without the catalytic additive when very bulky nucleophiles, such a *t*$BuNH_2$, as well as hydroxyl containing amides or amines were used.

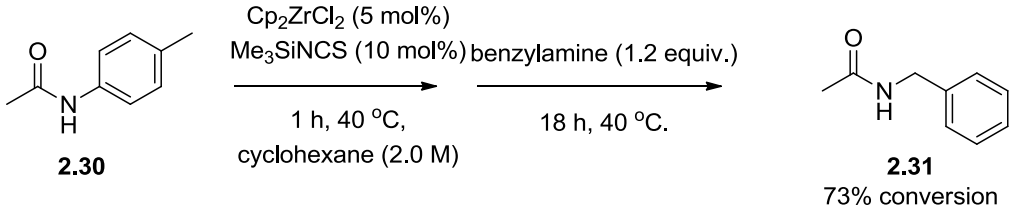
3.4.3 Secondary and Tertiary Amides

Both secondary and tertiary amides were shown to be much less reactive than primary amides for the acylation of benzylamine, during the previous investigations using just Cp_2ZrCl_2 (Chapter 2). Subsequently it was investigated as to whether using the optimised Cp_2ZrCl_2 and Me_3SiNCS catalytic combination would allow transamidation of secondary and tertiary amides. *N*-methylacetamide **2.32** and DMAC **2.33** were used as the secondary and tertiary amide species respectively (Scheme 58). 38% conversion into *N*-benzylacetamide **2.31** was observed when *N*-methylacetamide was used and no conversion was seen when DMAC was used.



Scheme 58. Transamidation of secondary and tertiary amides

The low conversion when *N*-methylacetamide **2.32** was used and no conversion when DMAC **2.33** was used (Scheme 58), highlights that the combined catalytic system of Cp_2ZrCl_2 and Me_3SiNCS is not only more catalytically active for primary amides it is now more selective over both secondary and tertiary alkyl amides. An explanation could be due to steric interactions being more influential, likely due to the lower temperature of the reaction. At this lower temperature there is less energy in the system to overcome the barrier of rotation around the amide bond and so minimise any interference with the catalyst.



Scheme 59. Transamidation of 4'-methylacetanilide with benzylamine

However, when 4'-methylacetanilide **2.30** was reacted under the same reaction conditions as *N*-methylacetamide and DMAC (Scheme 58), 73% conversion into the transamidated product was observed (Scheme 59). Interestingly this highlights a similar reactivity of *N*-aryl amides under the combined Cp_2ZrCl_2 and Me_3SiNCS catalyst system to that observed using our initial protocol only using Cp_2ZrCl_2 (Chapter 2).

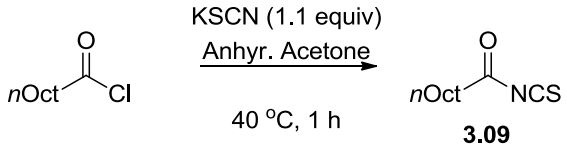
3.5 Mechanistic Investigations

In order to determine what role the addition of isothiocyanate was playing during the reaction the mechanism and role of the additive were investigated.

3.5.1 Investigations using Stoichiometric Isothiocyanate

It was shown previously that increasing the amount of isothiocyanate within the reaction reduced the overall conversion into product (Table 15) and produced significant amounts of unknown side products. This highlighted that isothiocyanate was not acting as a nucleophilic catalyst in the reaction, as an increase in conversion would be expected on increasing the amount of additive. However there was the possibility that an acylisothiocyanate could have been produced during the reaction due to the similarity of the splitting within the ^{1}H NMR to that of the starting amide.

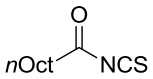
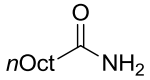
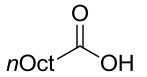
Synthesis of the acylisothiocyanate was undertaken in order to compare the ^{1}H NMR spectra of the reaction involving stoichiometric amounts of thiocyanate to a sample of acylisothiocyanate. *n*-Nonanoylisothiocyanate **3.09** was synthesised based on literature methods *via* displacement of the chloride of *n*-nonanoyl chloride with KSCN (Scheme 60).[100]



Scheme 60. Acylisothiocyanate synthesis

Acylisothiocyanates are known to be relatively unstable intermediates, undergoing polymerisation on prolonged standing and often require formation and use *in situ*.[101] After cannula filtration and removal of the solvent, the crude reactions were immediately analysed by ^{13}C NMR. Specifically the chemical shift of the carbonyl carbon was noted to indicate the formation of the acylisothiocyanate. The transamidation reaction, using stoichiometric Me_3SiNCS as an additive, was also repeated with *n*-nonamide **3.10** for ease of direct comparison of products

Table 17. ^{13}C NMR analysis of reaction products

Entry	Method of formation/ Carbonyl species	Observed ^{13}C NMR shift (ppm)
1	Crude synthesised **3.09** 	168.91
2	Pure **3.10** 	176.22
3	Pure **3.11** 	180.63
4	Stoichiometric use of Me_3SiNCS with amide	168.41

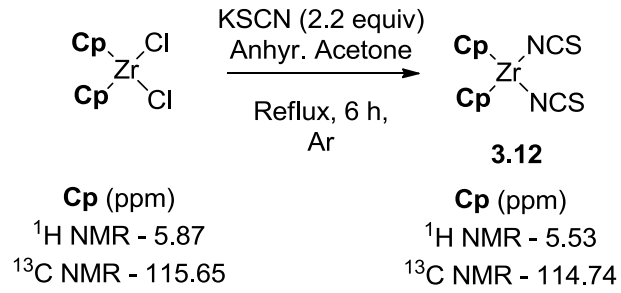
For ease of comparison, the ^{13}C NMR shift of the carbonyl of both *n*-nonamide **3.10** and *n*-nonanoic acid **3.11** were obtained. *n*-Nonamide and *n*-nonanoic acid showed ^{13}C NMR chemical shifts of 176.22 (Table 17, entry 2) and 180.63 (Table 17, entry 3) respectively for the carbonyl. These show a significant difference in chemical shift from the crude but directly synthesised *n*-nonanoylisothiocyanate with a chemical shift of 168.91 (Table 17, entry 1). A further difference in chemical shift was seen with the carbonyl containing species present after the use of a stoichiometric amount of Me_3SiNCS, which showed a chemical shift of 168.41 (Table 17, entry 1). Comparison of the carbonyl chemical shift after the transamidation reaction to that of the synthesised acylisothiocyanate clearly showed that *n*-nonanoylisothiocyanate was formed from *n*-nonamide.

It was also seen that, as noted previously with *n*-hexanamide (Table 15, entry 4), a low conversion of 34% into the *N*-benzyl nonamide was observed even though the acylisothiocyanate has been formed. This further confirms that the primary mechanism is not *via* nucleophilic displacement of the acylisothiocyanate by an amine. If this was the reaction mechanism, the reaction would not have proceeded at a slower rate than when a catalytic amount of Me_3SiNCS was used (Table 15, entry 1).

3.5.2 Isothiocyanate as a Ligand

It was investigated as to whether the isothiocyanate was acting, as our initial hypothesis proposed, as a ligand towards the zirconocene catalyst. A catalytic species that could have been formed, by the action of the additive on Cp_2ZrCl_2, was

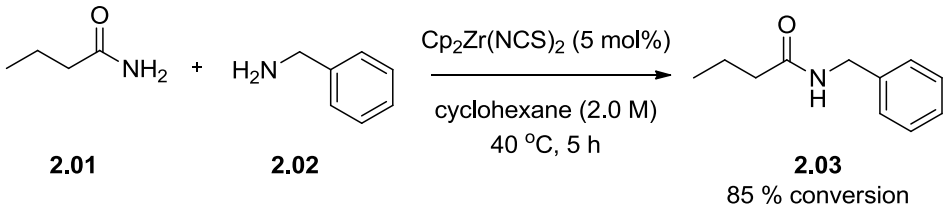
zirconocene diisothiocyanate ($Cp_2Zr(NCS)_2$) **3.12**. Therefore this species was synthesised *via* displacement of the chloride ligands of Cp_2ZrCl_2. The product isolated after the reaction showed an up field shift in the ^1H and ^{13}C NMR resonance of the Cp ligands in comparison with Cp_2ZrCl_2 (Scheme 61).



Scheme 61. Synthesis of $Cp_2Zr(NCS)_2$

The upfield shift observed was due to the increased back bonding from the isothiocyanate ligands on the zirconium. This shift also implies that the electron density on the zirconium would be increased so potentially altering the catalytic properties. The isolated compound **3.12** is known to be N- bound as opposed to S-bound, which can also be reasoned due the harder natured nitrogen, in comparison with the sulfur, pairing with the hard zirconium centre.

Using a catalytic amount of $Cp_2Zr(NCS)_2$ **3.12** (5 mol%) in the transamidation of *n*-butyramide with benzylamine, under the same reaction conditions as used previously, 85% conversion into product **2.03** was observed (Scheme 62).



Scheme 62. $Cp_2Zr(NCS)_2$ catalysed transamidation

Although a lower conversion was observed with $Cp_2Zr(NCS)_2$ (Scheme 62) than using a combination of Cp_2ZrCl_2 and Me_3SiNCS (Table 16, entry 1), it still showed higher catalytic activity than Cp_2ZrCl_2 (Table 13). The presence of the isothiocyanate ligands on the zirconocene could tune the Lewis acidity of the catalyst. As shown previously, isothiocyanate has been shown to generally have a stronger affinity for transition metals than chloride,[93] therefore the binding would be stronger. This

stronger binding would likely reduce the Lewis acidity of the zirconium due to the increased electron density on metal centre. Although reducing the Lewis acidity could create a weaker catalyst-amide interaction, a greater catalytic turnover could result. This reduced Lewis acidity was evident by the observed upfield shift in Cp ligands; this will be as a result of the increased back bonding of the NCS ligands in comparison with the Cl ligands.

3.6 Conclusions

Initially it was seen that using catalytic amounts of base to increase the catalyst efficiency, by forming *in situ* amidate complexes, proved unsuccessful. However it was found that on addition of catalytic amounts of additives the efficiency of the transamidation reaction was increased. After a screen of catalytic additives to form more active zirconocene complexes, Me_3SiNCS (10 mol%) was shown to give the highest increase in conversion. The transamidation reaction proceeded either at a lower temperature (40 °C) or in a shorter time (five hours) than without the catalytic additive. It was seen that in nearly all cases comparable or improved yields were obtained for the different substrates used, in comparison with the previously developed reaction conditions (Chapter 2). Synthesis and subjection of a potentially active catalytic species, $Cp_2Zr(NCS)_2$ **3.12**, to the transamidation reaction highlighted that it is likely to be the active catalyst formed *in situ.*

Chapter 4 –Catalytic Acylation of Alcohols Using Amides

"Scandium Triflate Catalysed Synthesis of Esters Using Primary Amides"
Atkinson, B.N.*; Williams, J. M. J., *Tetrahedron Lett.*, 2014, **55**, 6935-6938,
(Corresponding author)

Chapter 4: Results and Discussion III

4.1 Aims

The aim of this work was to investigate a methodology for the metal catalysed *O*-acylation of alcohols using amides as acylating agents.

The research detailed in this chapter follows on from previous work within the group which has focussed on the *N*-acylation of amines using amides as the acylating agents. This has been achieved using a variety of methods; as well those detailed in **Chapter 2** and **Chapter 3**.

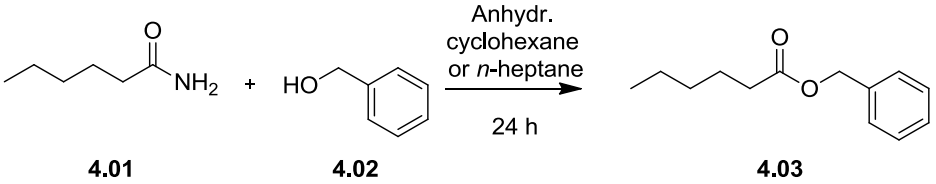
Therefore it was reasoned that a methodology could be developed that allowed amides to acylate alcohols as well as amines.

4.2 Catalyst Identification

Identification of a suitable catalyst began by examining the alcoholysis, at 10 mol% loading, of *n*-hexanamide **4.01** with benzyl alcohol **4.02** (Table 18).Initial use of a high catalyst loading (Table 18, entries 1-4) would amplify any potential catalytic activity of the metals used.

The initial catalysts used (Table 18, entries 1-4) had all shown precedence for activation of amides during our previous work using Cp_2ZrCl_2 (Chapter 2, Table 2). Interestingly no catalytic activity was observed when Cp_2ZrCl_2 was used (Table 18, entry 1). This continues the trend, seen with the substrate scope of the transamidation reaction that saw hydroxyl containing substrates reacting slowly or not at all. As zirconium is highly oxophilic the alcohol is likely acting as an inhibitor towards the catalyst.

Table 18. Catalyst identification[a]



4.01 **4.02** **4.03**

1.2 equiv

Entry	Catalyst (mol%)	Temp (°C)	Conversion into **4.03** (%)[b]
1	Cp_2ZrCl_2 (10)	80	0
2	$TiCl_4$ (10)	80	0
3	$Ti(OiPr)_4$ (10)	80	0
4	$Sc(OTf)_3$ (10)	80	53
5	$Sc(OTf)_3$ (5)	100	89
6	$Sc(OTf)_3$ (2.5)	100	71
7	$Y(OTf)_3$ (5)	100	28
8	$La(OTf)_3$ (5)	100	0
9	$Pr(OTf)_3$ (5)	100	0
10	$Gd(OTf)_3$ (5)	100	0
11	$Mg(OTf)_2$ (5)	100	0
12	TfOH (15)	100	23

[a]Reactions performed on 2 mmol scale with 2.4 mmol of alcohol in 2 mL of solvent. [b]Conversions determined by analysis of the crude ^{1}H NMR spectra

Titanium based species, notably $Ti(OiPr)_4$ and $TiCl_4$ (Table 18, entries 2 and 3), also showed no catalytic activity within the reaction. An explanation could be similar to that proposed for Cp_2ZrCl_2, in that strong binding of the alcohol to the $TiCl_4$ resulted in inhibition of the catalyst. When $Ti(OiPr)_4$ was used, displacement of the O*i*Pr ligands may not have occurred, resulting in no catalytic activity. However no isopropyl ester product was observed after the reaction. Only $Sc(OTf)_3$ showed any catalytic activity for the alcoholysis reaction (Table 18, entry 4) giving 53% conversion into **4.03**. Increasing the temperature to 100 °C and reducing the catalyst loading to 5 mol% gave 89% conversion (Table 18, entry 5) into ester **4.03**. On reducing the $Sc(OTf)_3$ catalyst loading to 2.5 mol%, a drop to 71% conversion was observed (Table 18, entry 6).

Based on the activity seen with $Sc(OTf)_3$ other lanthanide triflates were also investigated for catalytic activity. It has been reported in the literature that other lanthanide triflates have similar tolerances for both water and oxygen heteroatoms. However subtle differences in their catalytic activities have been seen depending on

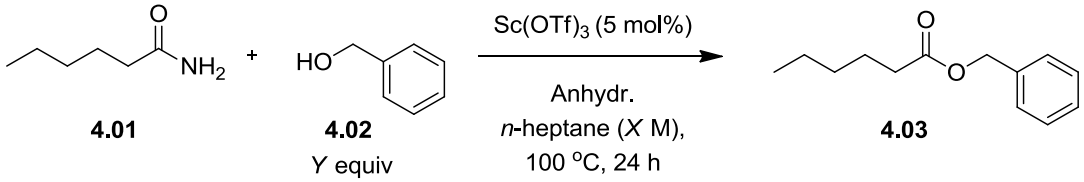
the reactants used.[102] The lanthanide triflates investigated included yttrium, lanthanum, praseodymium and gadolinium (Table 18, entries 9-12). Only yttrium showed any catalytic activity, albeit reduced in comparison with scandium, with 28% conversion (Table 18, entry 9). $Mg(OTf)_2$ was also investigated due to the diagonal relationship often noted between scandium and magnesium based on chemical reactivity, however no conversion was observed (Table 18, entry 11).

It was necessary to determine whether the catalytic activity was from $Sc(OTf)_3$ alone or whether trace TfOH was acting as the catalyst. If 5 mol% $Sc(OTf)_3$ was used, 15 mol% TfOH would be the theoretical maximum that could be present. Pleasingly, when TfOH (15 mol%) was used in the reaction only 23% conversion into ester **4.03** was observed (Table 18, entry 12) highlighting reaction dependence on $Sc(OTf)_3$.

4.3 Reaction Optimisation

In order improve the reaction towards quantitative conversion the effects of changing the reaction concentration and the amount of benzyl alcohol were investigated.

Table 19. Effect of concentration and alcohol equivalents



Entry	Concentration (M)	Benzyl alcohol equivalents	Conversion into 4.03 (%) [a]
1	1.0	1.2	89
2	2.0	1.2	72
3	1.0	1.0	85
4	1.0	1.4	82
5	1.0	1.6	77

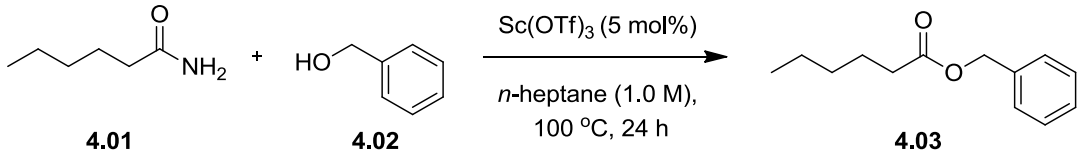
[a]Conversions determined by analysis of the crude ^{1}H NMR spectra

As observed previously (Chapter 3, Section 3.3) increasing the concentration of a reaction can further increase the conversion into product. It was seen that increasing the concentration of the reaction to 2.0 M decreased the conversion into product to 72% (Table 19, entry 2). As such the concentration of the reaction for further experiments was maintained at 1.0 M.

Altering the amount of benzyl alcohol could also affect the overall progress of the reaction. It was seen that on reducing the amount to one equivalent, a small drop to 85% conversion was observed (Table 19, entry 3). On increasing the amount of benzyl alcohol to 1.4 and 1.6 equivalents (Table 19, entries 4 and 5) a gradual decrease in conversion was observed with 82% and 77% respectively. Based on these results 1.2 equivalents of benzyl alcohol were used for all subsequent reactions.

After this the tolerance of the reaction towards water was investigated by using either reagent grade or anhydrous solvents as well using a sample of dried catalyst (Table 20).

Table 20. Effects of adventitious water



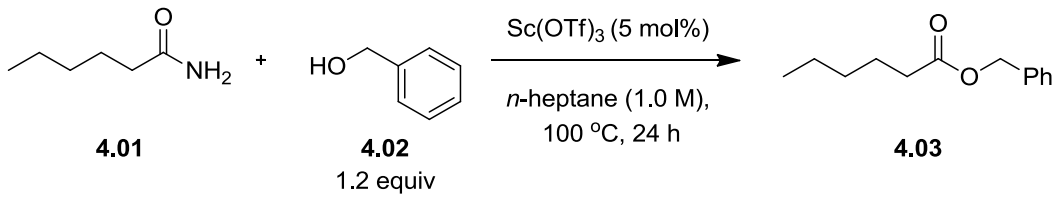
4.01 **4.02** 1.2 equiv **4.03**

Entry	Dried Catalyst[a]	Solvent	Conversion into 4.03 (%)[b]
1	No	Anhydr.	89
2	Yes	Anhydr.	80
3	No	Reagent grade	95
4[c]	No	Reagent grade	98

[a]Dried in an open flask at 200 °C for 18h. [b]Conversions determined by analysis of the crude ^{1}H NMR spectra. [c]Reaction carried out in an open reaction vessel.

Interestingly when a sample of $Sc(OTf)_3$ was dried at 200 °C for 18 hours and used in the reaction, conducted in anhydrous solvent, a decrease in conversion was seen to 80% (Table 20, entry 2). Subsequent to this, simply using reagent grade *n*-heptane instead of anhydrous *n*-heptane gave an increase to 95% conversion (Table 20, entry 3). A further increase to 98% was seen when the reaction was carried out open to the air (Table 20, entry 4)

Table 21. Addition of water



4.01 **4.02** 1.2 equiv **4.03**

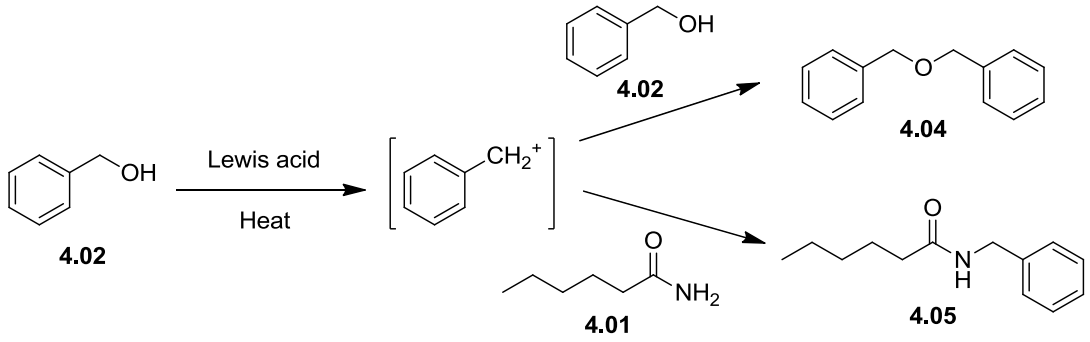
Entry	H_2O Equivalents	Conversion into 4.03 (%)[a,b]
1	0	98
2	0.5	87
3	1	85
4	2	74

[a] Conversions determined by analysis of the crude ^{1}H NMR spectra
[b] Reaction carried out in an open reaction vessel

To investigate whether water was playing a key role in the reaction a series of experiments was carried out with increasing amounts of water present. On addition of water a small decrease in conversion to 87% (Table 21. entry 2) and 85% (Table 21. entry 3) was seen with either half an equivalent or one equivalent respectively. On further increasing the amount of water to two equivalents, the conversion dropped further to 74% (Table 21. entry 4). Although these results showed that excess water does reduce the overall conversion it highlighted the high tolerance of the methodology towards water, as complete catalyst inhibition was not observed.

4.3.1 Side Products

A number of side products might be formed during the course of the reaction. Benzyl alcohol could, under Lewis acid catalysis, undergo formation of a benzyl carbocation. Addition of a nucleophile to this would result in the formation of either dibenzyl ether **4.04** or *N*-benzyl hexanamide **4.05** (Scheme 63). Both of which can be identified by, but were not observed in any, ^{1}H NMR spectra during the optimisation of the reaction. Another side product could be the Lewis acid catalysed hydrolysis of *n*-hexanamide to yield *n*-hexanoic acid, however this was not observed during the reaction optimisation.



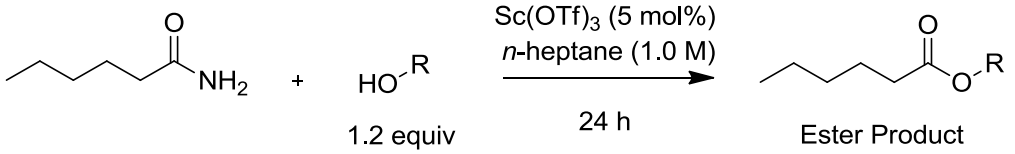
Scheme 63. Potential side products

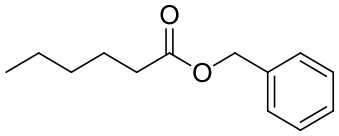
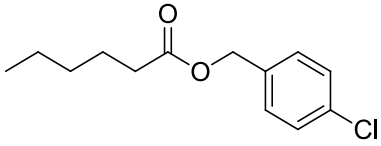
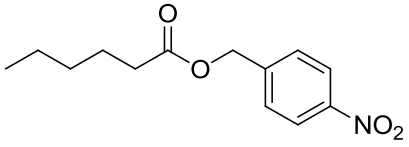
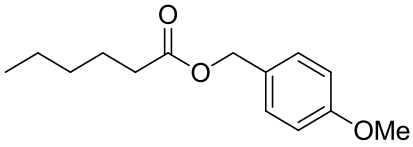
4.4 Substrate Scope

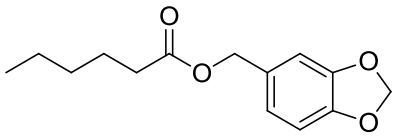
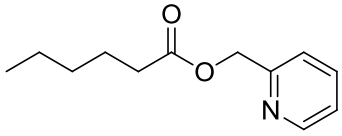
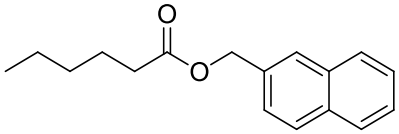
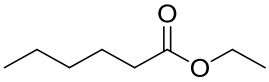
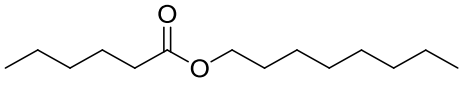
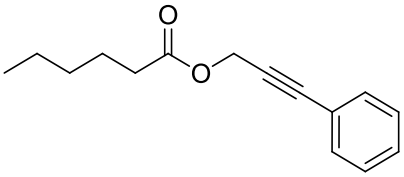
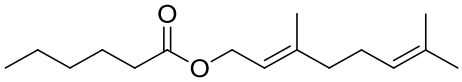
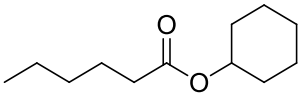
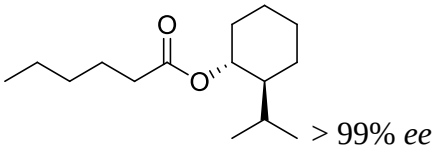
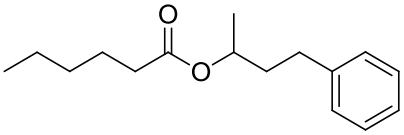
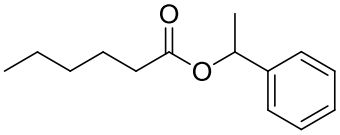
Using the optimised reaction conditions with $Sc(OTf)_3$ (5 mol%) and *n*-heptane as the solvent, the substrate scope of the reaction was investigated .

4.4.1 Alcohol Substrate Scope

Table 22. Alcoholysis scope using *n*-hexanamide[a]



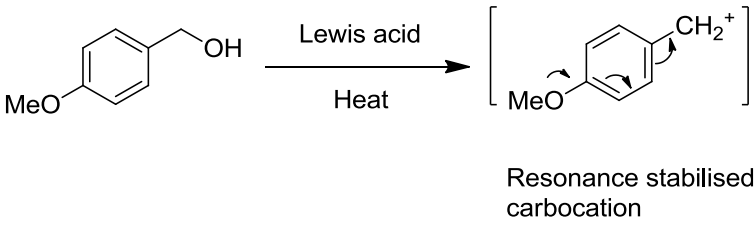
Entry	Ester Product		Temp (°C)	Yield (%)[b]
1		**4.03**	100	90 (98)
2		**4.06**	100	83 (92)
3		**4.07**	100	48 (53)
4		**4.07**	100	- (55)/13[c]

5		**4.08**	100	74 (80)/1.5[c]
6		**4.09**	100	- (28)
7		**4.10**	100	93 (99)
8		**4.11**	100	-(36)
9		**4.12**	100	91 (98)
10		**4.13**	100	82 (87)
11		**4.14**	100	85 (93)
12		**4.15**	100 125[d]	- (34) 84 (90)
13	 > 99% *ee*	**4.16**	125[d]	72 (80)
14		**4.17**	125[d]	83 (88)
15		**4.18**	125[d]	-(70)/11[c]

[a]Reactions performed on 2 mmol scale with 2.4 mmol of alcohol in 2 mL of solvent. [b]Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra. [c]Conversion into corresponding symmetrical ether. [d]Reaction carried out in *n*-octane.

The alcoholysis of *n*-hexanamide with a variety of benzyl alcohols afforded the corresponding esters in moderate to excellent yields. The parent reaction with benzyl alcohol produced a 90% yield of the corresponding ester (Table 22, entries 1). Use of benzyl alcohols with electron withdrawing groups on the aryl ring gave reduced

yields of products, likely due to reduced nucleophilicity of the alcohol (Table 22, entries 2 and 3). With electron rich alcohols it was seen that a significant amount of the symmetrical ether was formed, notably with 4-methoxybenzyl alcohol only 55% conversion into product and 13% conversion into the corresponding symmetrical ether was observed (Table 22, entry 4). A possible explanation is due to the formation of the benzylic carbocation that is stabilised by the presence of the electron donating methoxy group (Scheme 64). Subsequent nucleophilic attack by another molecule of 4-methoxybenzyl alcohol on the formed carbocation would lead to the symmetrical ether. The propensity of 4-methoxybenzyl alcohol to form a stabilised carbocation has been used in the literature to prepare *para*-methoxybenzyl (PMB) ethers, a common protecting group.[103]



Scheme 64. Formation of resonance stabilised 4-methoxybenzyl alcohol carbocation

Interestingly, when piperonyl alcohol was used, a much cleaner reaction was seen with only 1.5% symmetrical ether produced (Table 22, entry 5). Other benzylic alcohols also reacted cleanly with 2-naphthylenemethanol producing a 93% yield of the corresponding ester (Table 22, entry 7). However when 2-pyridinemethanol was used only 28% conversion was seen (Table 22, entry 6), this was likely due to the very low solubility that was observed for 2-pyridinemethanol in the reaction solvent. When a straight chain, aliphatic alcohol such as *n*-octanol was used, a clean reaction and high yield of 91% was obtained (Table 22, entry 9). However use of a shorter chain aliphatic alcohol, ethanol, resulted in a low conversion of 36% (Table 22, entry 8). Due to the high reaction temperature of 100 °C, it is likely that as ethanol's boiling point is 78 °C it was lost from the reaction medium during the prolonged heating.

Following on from this, alcohols that have the potential to form stabilised carbocations were investigated. These included the alkynol, 3-phenylpropyn-1-ol, and the alkenol, geraniol. Although the former, propargylic carbocation is formed less readily than either the benzylic or allylic carbocation, under Lewis acidic

conditions it is known to react with nucleophiles.[104] However in both cases the corresponding alkynyl and allyl esters were produced in good yields of 82% and 85% respectively (Table 22, entries 10 and 11) without symmetrical ether formation.

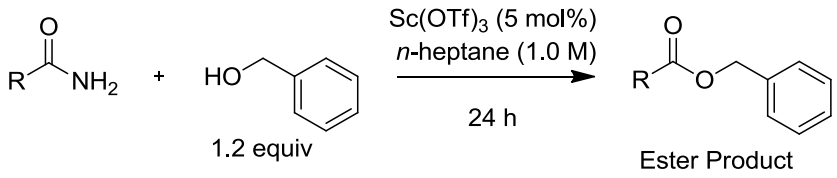
Secondary alcohols required elevated temperatures of 125 °C as at 100 °C, using cyclohexanol, only 34% conversion into ester product was observed (Table 22, entry 12). This is likely to be due to the increased steric bulk around the hydroxyl hindering the reactivity. Switching the reaction solvent to *n*-octane, allowed for an increase in temperature and produced the ester product in an 84% yield (Table 22, entry 12). Continuing with this elevated temperature, acyclic and cyclic secondary alcohols could be converted into ester products in good yields. L-Menthol, even though the steric bulk around the hydroxyl is further increased due to the close proximity to the isopropyl group, reacted cleanly giving the ester product in a 72% yield (Table 22, entry 13). The enantiomeric purity of >99% *ee* was maintained throughout the reaction, as determined by HPLC by comparison with the racemic ester. Other secondary alcohols such as 4-phenyl-butan-2-ol also gave good yields, producing an 83% yield of the corresponding ester product (Table 22, entry 14).

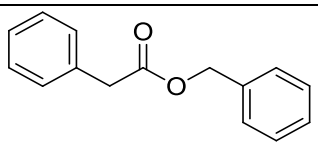
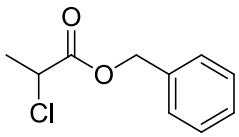
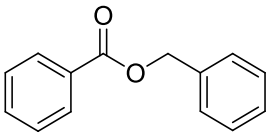
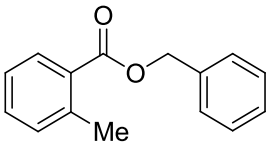
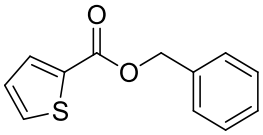
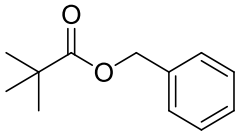
When secondary benzylic alcohols were used, such as 1-phenylethanol, a significant amount of symmetrical ether was observed (Table 22, entry 14) as although a 70% conversion was seen, 11% of the symmetrical ether was also produced. The carbocation formed from 1-phenyethanol would be a secondary benzylic carbocation and therefore, in a similar manner to that observed for 4-methoxybenzyl alcohol (Table 22, entry 4), would be a relatively stabilised carbocation. It has been reported that 1-aryl ethanols, in combination with a lanthanide triflate catalyst, undergo Friedel-Crafts alkylation reactions in combination with aromatic nucleophiles such as toluene.[105] However in this case the remaining 1-phenylethanol reacts with the carbocation to produce the symmetrical ether.

4.4.2 Amide Substrate Scope

Using the optimised reaction conditions the $Sc(OTf)_3$ catalysed alcoholysis of various primary amides was investigated using benzyl alcohol (Table 23).

Table 23. Alcoholysis scope using benzyl alcohol[a]



Entry	Ester Product		Temp (°C)	Yield (%)[b]
1		**4.19**	100	94 (99)
2		**4.20**	100	55 (59)
3		**4.21**	100 125[c]	- (23) 78 (82)
4		**4.22**	125	-(0)
5		**4.23**	125[c]	71 (78)
6		**4.24**	125[c]	39 (46)

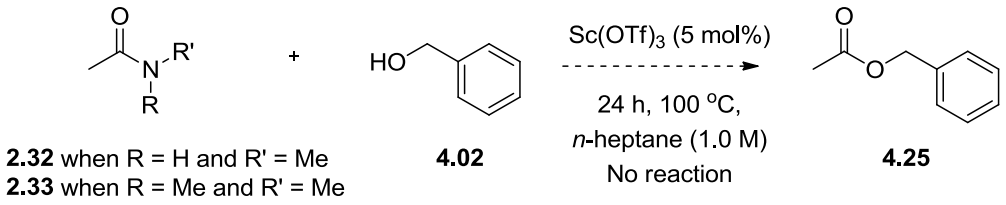
[a]Reactions performed on 2 mmol scale with 2.4 mmol of alcohol in 2 mL of solvent. [b]Isolated yield; figures in parentheses are conversions determined by analysis of the ^{1}H NMR spectra. [c]Reaction carried out in *n*-octane.

2-Phenylacetamide reacted cleanly to give 94% yield of ester product (Table 23, entry 1). Alkyl halides were also tolerated with 2-chloropropionamide giving a modest yield of 55% of the corresponding benzyl ester (Table 23, entry 2). Higher temperatures were required for more chemically robust amides, as seen during the investigations of the substrate scope for the transamidation reaction (Chapter 2, Section 2.5.1), due to the reduced electrophilicity of the aromatic amides. However on use of *n*-octane as the reaction solvent and an elevated temperature of 125 °C, a good yield of 78% was obtained from benzamide (Table 23, entry 3). Interestingly

no reaction was seen when 2-methylbenzamide was subjected to the reaction conditions, possibly due to steric interactions with the catalyst. This showed an incompatibility with 2-substituents on the aryl ring, a point also noted with the transamidation reaction investigated previously (Chapter 2, Section 2.5.1). Small heterocycles were also tolerated; with thiophene-2-carboxamide producing 71% of the corresponding ester (Table 23, entry 5). Unfortunately even at the elevated temperature of 125 °C only 39% yield of benzyl pivalate was obtained (Table 23, entry 6). This is likely to be due to the steric bulk around the amide reducing the susceptibility towards nucleophilic attack.

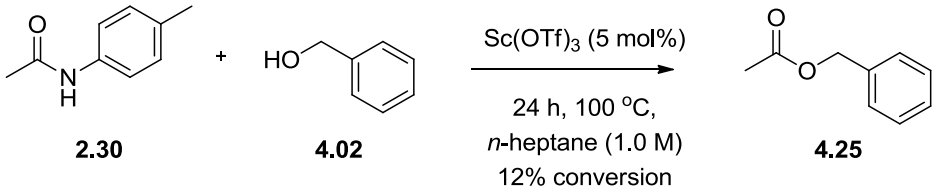
4.4.3 Secondary and Tertiary Amides

Secondary and tertiary amides were subjected to the reaction conditions to identify whether the methodology was selective for primary amides. On reacting *N*-methylacetamide **2.32** and DMAC **2.33** with benzyl alcohol under the optimised reaction conditions, it was seen that no conversion into benzyl acetate **4.25** was observed (Scheme 65). This highlights the high selectivity of the reaction conditions for primary amides over both secondary and tertiary amides. As noted previously (Chapter 2, Section 2.5.3) the selectivity could be due to unfavourable interactions of the *N*-alkyl groups either inhibiting catalyst binding or reducing the susceptibility to nucleophilic attack.



Scheme 65. Alcoholysis of secondary and tertiary amides

Following on from this an *N*-aryl amide, 4'methylacetanilide **2.30**, was subjected to the reaction conditions. The loss of the resonance stabilised amine was shown to be favourable under the Cp_2ZrCl_2 catalysed transamidation conditions as discussed previously (Chapter 2, Section 2.5.3). However it was seen that when 4'methylacetanilide was reacted with benzyl alcohol only 12% conversion into the ester product **4.25** occurred (Scheme 66)



Scheme 66. Alcoholysis of 4'-methylacetanilide

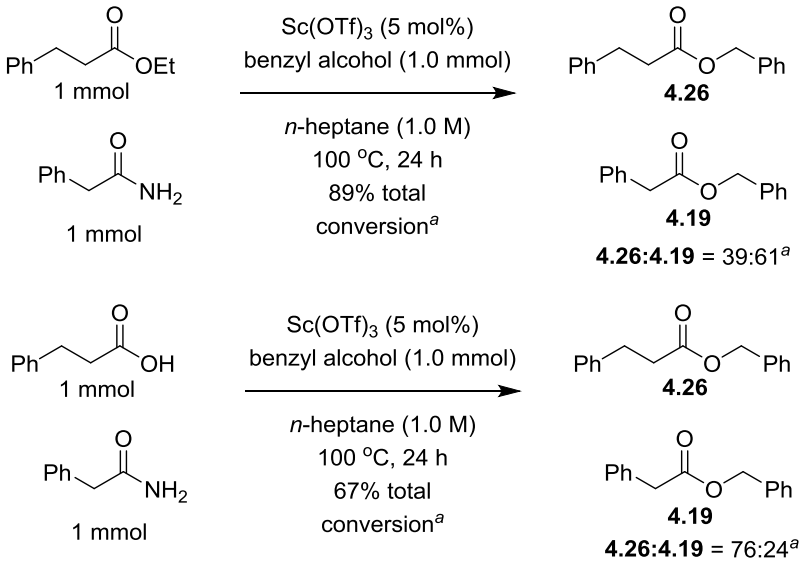
4.4.4 Reaction Limitations

Notable limitations were encountered when the substrate scope was explored. Phenols were shown to be unreactive under the catalytic conditions, returning the starting materials after the reaction. This is likely to be due to the significantly reduced nucleophilicity of phenols in comparison with the other alcohols explored. During the previous work carried out for the development of a transamidation reaction it was observed that formamide and 2,2,2-trifluoroacetamide required only 30 °C to produce transamidated products (Chapter 2 Section 2.5.2). However on subjecting formamide and 2,2,2-trifluoroacetamide to the optimised $Sc(OTf)_3$ catalysed amide alcoholysis reaction conditions, little conversion into the ester product was observed. Despite the favourable reactivity previously observed the high reactivity of the formed formyl or 2,2,2-trifluoroacetyl esters could undergo reaction back into the starting primary amide. Another possible explanation could be due the lack of interaction of the catalyst with the primary amide. Formamide and 2,2,2-trifluoroacetamide will have reduced Lewis basicity of the carbonyl oxygen so catalyst binding could be reduced, so reducing the conversion into product.

4.5 Competition Reactions

Competition reactions were carried out in order to determine a relative reactivity, in comparison with carboxylic acids and esters (Scheme 67). It was observed that in a direct competition reaction of ethyl hydrocinnamate and 2-phenylacetamide with one equivalent of benzyl alcohol, 89% total conversion into benzyl ester products was seen (Scheme 67). Of the converted starting materials, a 61:39 ratio of amide alcoholysis product **4.19** to transesterified product **4.26** was seen indicating greater reactivity of the amide over the ester. When a similar competition reaction was carried out between hydrocinnamic acid and 2-phenylacetamide a lower total conversion of 67% was observed (Scheme 67). Interestingly in contrast to the reaction carried out with the ester, it was seen that the esterification of the carboxylic

acid proceeded more quickly than the alcoholysis of the primary amide with 76:24 ratio of the esterified product **4.26** to the amide alcoholysis product **4.19**. Therefore under these reaction conditions a general reactivity series could be proposed; carboxylic acid > primary amide > ester.



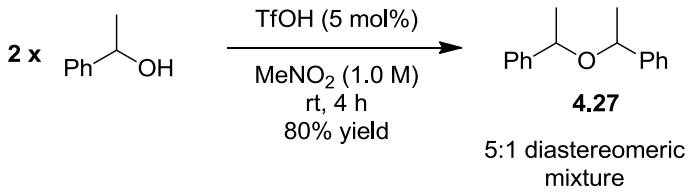
[a]Conversion determined by analysis of the crude ^{1}H NMR spectra.

Scheme 67. Competition reactions with carboxylic acids and esters

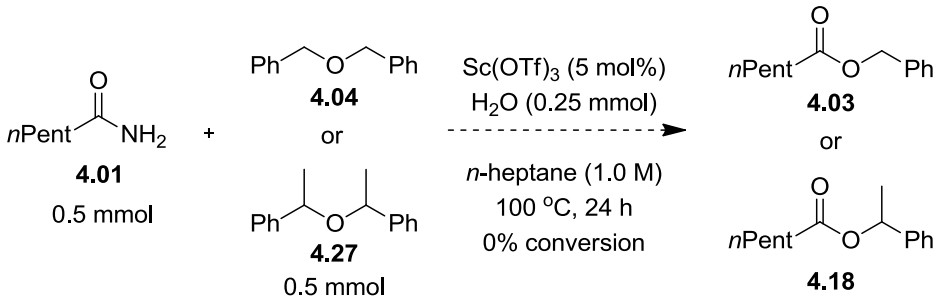
Under these same reaction conditions (Scheme 67) 100% conversion was observed for the direct Fischer-Speier esterification of hydrocinnamic acid and 87% conversion was observed for the transesterification of ethyl hydrocinnamate.

4.6 Elucidation of Water's Role

During optimisation of the reaction conditions, the use of reagent grade solvent instead of anhydrous solvent gave a higher conversion into product. Although not observed in the ^{1}H NMR spectra after the reaction, any dibenzyl ether that was formed as a side product could be fragmented by the adventitious water so reforming the benzyl alcohol. To investigate this dibenzyl ether **4.04** and diaryl ether **4.27**, synthesised from 1-phenylethanol (Scheme 68), were subjected to the reaction conditions with 0.5 equivalents of water present. However in both cases no conversion into ester product was observed (Scheme 69), therefore highlighting that ether formation and subsequent fragmentation does not take place in the reaction.



Scheme 68. Diarylether synthesis



Scheme 69. *n*-Hexanamide reaction with symmetrical benzyl ether

4.7 NMR Studies

NMR studies were undertaken to elucidate a potential mechanism of the reaction. To a 1:1 mixture of *n*-hexanamide to *n*-octanol in $CDCl_3$ at 25 °C, increasing amounts of $Sc(OTf)_3$ were added. The initial 1:1 mixture showed a single broad singlet for the primary amide NH's at 6.22 ppm (Figure 6, **A**). On addition of 5 mol% aliquots of $Sc(OTf)_3$ a down field shift was observed for the amide NH signals on each addition (Figure 6, **B** and **C**). To highlight further that the scandium was binding to the amide it was observed that the α-protons of the amide were also seen to shift downfield. The observed shift of the α-protons changed from 2.10 ppm (Figure 6, **A**) to 2.15 ppm and 2.19 ppm respectively (Figure 6, **B** and **C**)

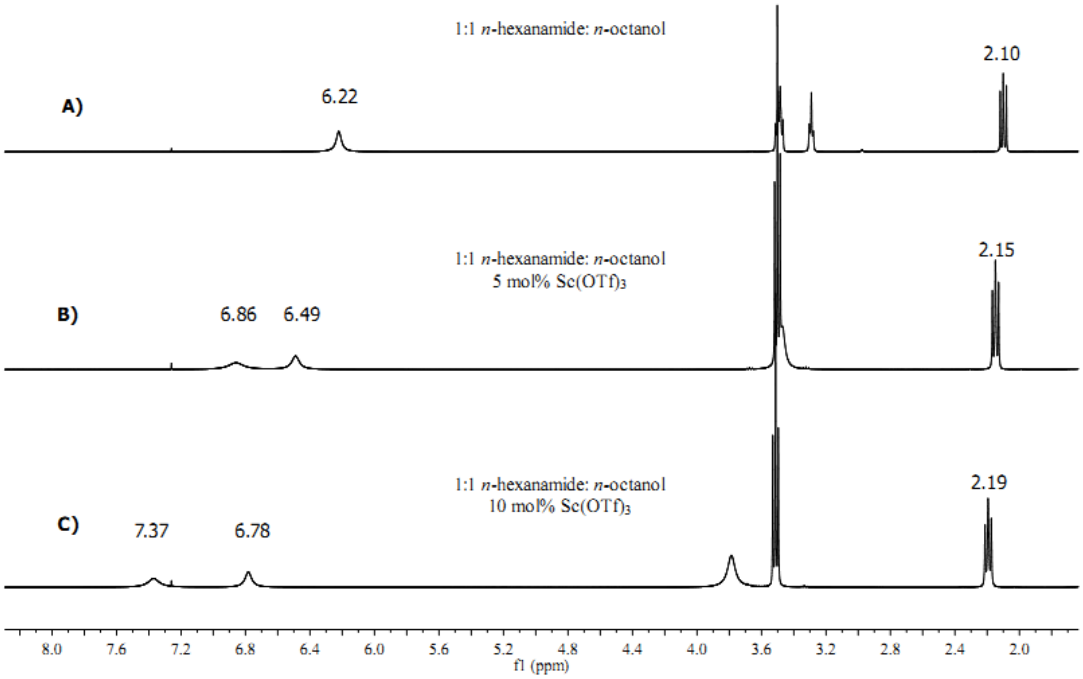


Figure 6. ^{1}H NMR spectra of $Sc(OTf)_3$ addition to 1:1 mixture of *n*-hexanamide and *n*-octanol

To confirm the idea that the scandium is increasing the susceptibility of the carbonyl to nucleophilic attack by increasing its electrophilicity the ^{13}C NMR spectra of the samples were also taken. A resonance of 176.69 was observed for the amide carbonyl in the sample where no scandium was present (Figure 7, **A**). On addition of increasing amounts of $Sc(OTf)_3$ a downfield shift was observed for the carbonyl to 177.79 with 5 mol% $Sc(OTf)_3$ (Figure 7, **B**) and 178.70 with 10 mol% $Sc(OTf)_3$ (Figure 7, **C**).

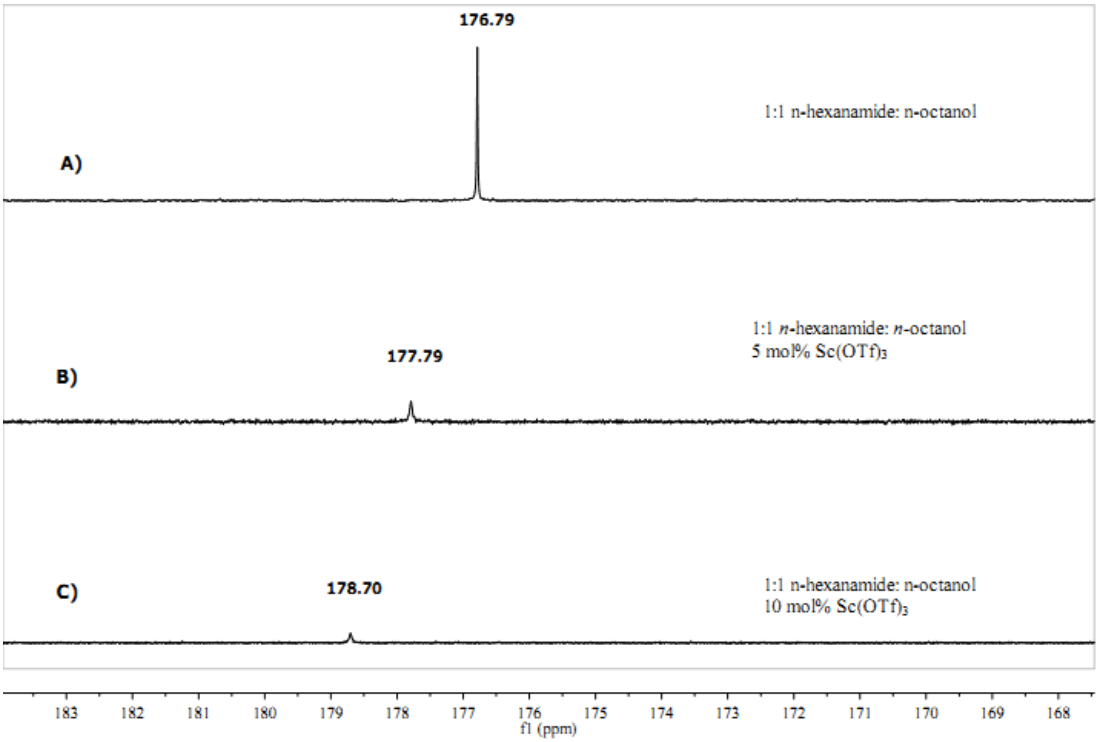


Figure 7. ^{13}C NMR spectra of $Sc(OTf)_3$ addition to 1:1 mixture of *n*-hexanamide and *n*-octanol

The deshielding of the carbonyl carbon by the scandium was observed on analysis of both the ^{1}H and ^{13}C NMR spectra. This clearly indicated the binding of the scandium to the amide, so increasing the electrophilicity of the carbonyl and susceptibility towards nucleophilic attack. The observed ^{1}H and ^{13}C spectra also highlight that catalyst binding to the amide is reversible on the NMR timescale with an averaging of the bound and free amide observed in the spectra at room temperature.

4.8 Proposed Mechanism

The proposed mechanism begins with initial coordination of the scandium centre to the primary amide to give intermediate **A** (Figure 8). Adventitious water, which was shown to benefit the reaction (Table 20), could aid this coordination of the scandium towards the amide. This was reasoned from crystal structures of the hydrates of $Sc(OTf)_3$ that have been shown to adopt tricapped trigonal prisms, with water molecules displacing triflates from the first coordination sphere, so allowing donor molecules to compete for the capping positions.[106] Subsequent attack by the alcohol on to the amide carbonyl, facilitated by the increased electrophilicity which was evident by NMR data, could lead to a short lived oxonium containing species, **B**. A

proton transfer process would likely lead from **B** to the ammonium species **C**. This would then undergo rapid elimination of ammonia followed by dissociation of the ester product, completing the catalytic cycle.

As such the mechanism could be considered analogous to that of the Fischer-Speier esterification of carboxylic acids, *via* activation of the amide to nucleophilic attack through carbonyl coordination. However in this case the significantly low solubility of ammonia in the reaction solvent, as well as the temperature at which the reactions are carried out, will also favour the equilibrium towards product formation *via* loss of ammonia from the reaction system.

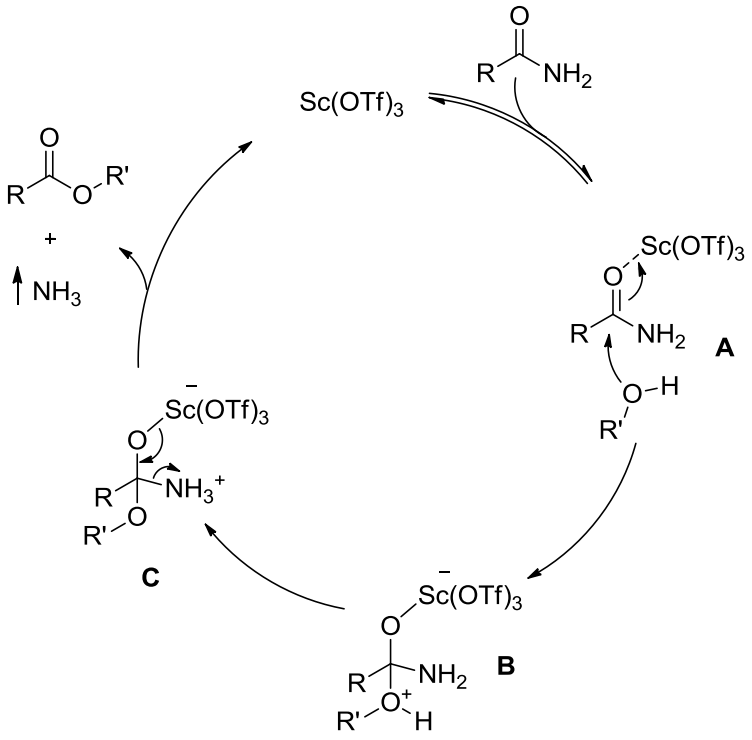


Figure 8. Possible catalytic cycle of a $Sc(OTf)_3$ catalysed acylation of alcohols using primary amides

4.9 Conclusions

In conclusion we have developed a $Sc(OTf)_3$ catalysed methodology for the alcoholysis of primary amides with alcohols. By proceeding in aliphatic hydrocarbon solvents only 1.2 equivalents of alcohol were required for alcoholysis of primary amides. As such this method provides a complementary method to existing protocols

where using the reacting alcohol as the reaction medium would not be feasible. Competition reactions showed that primary amides displayed greater reactivity, under these conditions, towards nucleophilic acylation reactions than esters. Mechanistic studies also revealed activation of the primary amide by the scandium, demonstrated by analysis of both ^{1}H and ^{13}C NMR spectra.

Chapter 5: Experimental

5.1 General Materials and Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under a nitrogen atmosphere using evacuated carousel tubes or ampoules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Acros Organics, Aldrich, Alfa Aesar, Fluka, Lancaster, Maybridge, Strem or TCI UK and used without further purification. Thin layer chromatography was carried out on aluminium or plastic backed silica plates, purchased from Aldrich. The plates were visualised under UV (254 nm) light, followed by staining with phosphomolybdic acid dip or potassium permanganate and gentle heating. During compound separations, column chromatography was carried out using 60 micron dry silica purchased from Aldrich. Organic layers were routinely dried with anhydrous $MgSO_4$ and concentrated using a Büchi rotary evaporator.

^{1}H NMR / ^{13}C NMR spectra were run in deuterated (≥99.5%) solvents purchased from Fluorochem unless stated otherwise, on either a Bruker Avance 250 (250 MHz) or a Bruker Avance 300 (300 MHz). Any chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δH = 0.00 ppm) unless otherwise stated. The coupling constants (*J*) are reported in Hz and signal multiplicities are reported as singlet (s) , doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sext), septet (sept), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), or broad singlet (br. s).

For mass spectrometry data acquisition a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik, GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an autosampler only. 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with relevant absorbances quoted as ν in cm^{-1}. Optical rotations were measured on an AA-10 Automatic Polarimeter. Enantiomeric excess was measured using a Perkin Elmer 200 Series HPLC machine, eluting with HPLC grade *n*-hexane and *i*PrOH using a ratio and Chiracel column as specified for each compound. Melting point's were determined using Stuart SMP10 melting point equipment using closed end glass capillary tubes and are uncorrected.

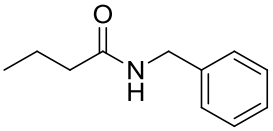
5.2 Chapter 2 Experimental Methods and Compound Characterisation

General Procedure I. Catalyst Screening and Optimisation (Chapter 2, Section 2.2 and 2.3): *n*-Butyramide (87 mg, 1 mmol) was added to an oven dried Radleys carousel tube. To this benzylamine (109 µL, 1 mmol), the appropriate catalyst (5 or 10 mol% see **Table 2**) and solvent (1 mL) was added and the tube sealed and heated for 18 hours at reflux. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo*. When necessary Quadrasil AP was added to a suspension of the crude product in DCM and stirred for one hour to remove NMR active catalytic species, organics filtered and solvent removed *in vacuo*. The crude reaction mixtures were analysed by their ^{1}H NMR spectra.

General Procedure II. *N*-Acylation of Amines with Amides: An oven dried Radleys carousel tube was charged with amide species (one equivalent, if amide was solid), amine (1.2 equivalents, unless otherwise stated, if amine was solid), Cp_2ZrCl_2 (5 mol%) and the tube was sealed and purged with nitrogen gas for around 10 minutes. After which a solution of anhydrous cyclohexane or heptane, volume as appropriate, containing the amide species (one equivalent, if amide was a liquid) and/or the amine species (1.2 equivalents, if amine was a liquid) was added to the reaction tube and the reaction heated at reflux or 30 °C (see Table 7 or Table 8). After being allowed to cool to room temperature the reaction is quenched using 5 mL of MeOH and the solvent was removed *in vacuo* on a rotary evaporator. Unless otherwise stated, DCM (50 mL) was added and the organics washed with water (20 mL). The organics were separated and the aqueous washed with DCM (2 x 50 mL), the organics were combined and dried over $MgSO_4$. Volatiles were removed *in vacuo*

and the crude reaction mixture was the analysed by ^{1}H NMR and ^{13}C NMR spectra and mass spectrometry data. Purification by column chromatography and recrystallisation was carried out as necessary.

2.03. *N*-Benzylbutyramide[107] (Table 7, Entry 1)



Following general procedure II, *n*-butyramide (3.0 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (468 mg, 88% yield) after column chromatography (eluting with DCM/MeOH 95:5) and recrystallisation (DCM/Hex).

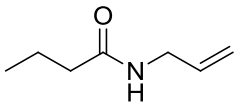
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.20 (5H, m, Ph), 6.01 (1H, br. s, NH), 4.38 (2H, d, *J* = 5.7 Hz, $NHCH_2Ph$), 2.15 (2H, t, *J* = 7.5 Hz, $CH_2CH_2C(O)$), 1.64 (2H, sext., *J* = 7.4 Hz, $CH_3CH_2CH_2$), 0.92 (3H, t, *J* = 7.4 Hz, CH_3CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 138.5, 128.7, 127.8, 127.4, 43.5, 38.6, 19.2, 13.8.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1631 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_{11}H_{15}NOH]^{+}$: 178.1232. Found: 178.1248.

2.06. *N*-Allylbutyramide[16] (Table 7, Entry 2)



Following general procedure II, *n*-butyramide (3.0 mmol, 261 mg) was used as the amide species and allylamine (3.6 mmol, 270 µL) as the amine species. The *title compound* was recovered as a orange oil (347 mg, 91% yield) after column chromatography (eluting with DCM/MeOH 95:5).

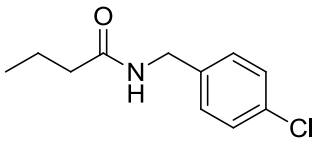
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.11 (1H, br. s, NH), 5.83 – 5.70 (1H, m, CH_2CHCH_2), 5.14 – 5.01 (2H, m, CH_2CHCH_2), 3.80 (2H, tt, *J* = 5.7, 1.5 Hz, $CHCH_2NH$), 2.12 (2H, t, *J* = 7.4 Hz, $CH_2CH_2C(O)$), 1.60 (2H, sext., *J* = 7.4 Hz, $CH_3CH_2CH_2$), 0.86 (3H, t, *J* = 7.5 Hz, CH_3CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 134.4, 116.0, 41.8, 38.5, 19.2, 13.7.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1639 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_7H_{13}NONa]^+$: 150.0895. Found: 150.0913.

2.07. *N*-(4-Chlorobenzyl)butyramide[16] (Table 7, Entry 3)



Following general procedure II, *n*-butyramide (3.0 mmol, 261 mg) was used as the amide species and 4-chlorobenzylamine (3.6 mmol, 438 µL) as the amine species. The *title compound* was recovered as a white solid (564 mg, 89% yield) after column chromatography (eluting with DCM/MeOH 92:8) and recrystallisation (DCM/Hex).

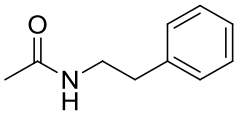
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (2H, d, *J* = 8.4 Hz, 2 x CHC<u>H</u>Cl), 7.20 (2H, d, *J* = 8.4 Hz, 2 x C<u>H</u>CHCl), 5.89 (1H, br. s, N<u>H</u>), 4.39 (2H, d, *J* = 5.8 Hz, C<u>H</u>$_2$Ar), 2.19 (2H, t, *J* = 7.5 Hz $CH_2C\underline{H}_2C(O)$), 1.67 (2H, sext., *J* = 7.5 Hz, $CH_3C\underline{H}_2CH_2$), 0.95 (3H, t, *J* = 7.5 Hz, C<u>H</u>$_3$CH$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 137.0, 133.3, 129.1, 128.8, 42.8, 38.6, 19.2, 13.8,

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1634 (C=O stretch).

HRMS (ESI-TOF) calcd for $[C_{11}H_{14}ClNOH]^+$: 212.0842. Found: 212.0842

2.08. *N*-Phenethylacetamide[108] (Table 7, Entry 4)

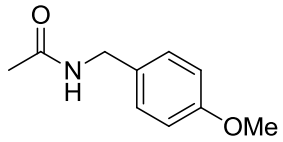


Following general procedure II, acetamide (236 mg, 4 mmol) was used as the amide species and 2-phenylethylamine (605 µL, 4.8 mmol) as the amine species. The *title compound* was recovered as an off-white solid (509 mg, 78% yield) after column chromatography (eluting with DCM/MeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 - 7.09 (5H, m, Ph), 5.98 (1H, br. s, N<u>H</u>), 3.40 (2H, q, *J* = 7.0 Hz, NHC<u>H</u>$_2$CH$_2$), 2.72 (2H, t, *J* = 7.1 Hz, $CH_2C\underline{H}_2$Ph), 1.84 (3H, s, $CH_3C(O)$).

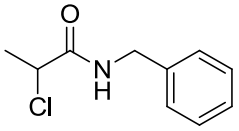
^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 139.0, 128.7, 128.6, 126.5, 40.8, 35.6, 23.3.
IR(neat): $\bar{\nu}$ (cm^{-1}) = 1638 (C=O stretch).
HMRS(ESI-TOF) calcd of $[C_{10}H_{13}NOH]^+$: 164.1075.Found: 164.1079.

2.09. *N*-(4-Methoxybenzyl)acetamide[109] (Table 7, Entry 5)



Following general procedure II, acetamide (236 mg, 4 mmol) was used as the amide species and 4-methoxybenzylamine (627 µL, 4.8 mmol) as the amine species. The *title compound* was recovered as an orange solid (581 mg, 81% yield) after column chromatography (eluting with DCM/MeOH 10:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (2H, d, *J* = 8.7 Hz, 2 x Ar C<u>H</u>), 6.87 (2H, d, *J* = 8.7 Hz, 2 x Ar C<u>H</u>), 5.79 (1H, br. s, N<u>H</u>), 4.36 (2H, d, *J* = 5.7 Hz, NHC<u>H_2</u>Ph), 3.80 (3H, s, ArOC<u>H_3</u>), 2.01 (3H, s, $CH_3C(O)$).
^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 159.1, 130.2, 129.2, 114.0, 55.3, 43.2, 23.2.
IR(neat): $\bar{\nu}$ (cm^{-1}) = 1628 (C=O stretch).
HRMS(ESI-TOF) calcd for $[C_{10}H_{13}NO_2H]^+$: 180.1025. Found: 180.1017.

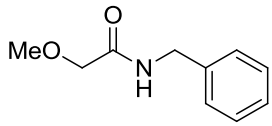
2.10. (±)-*N*-Benzyl-2-chloropropionamide[110] (Table 7, Entry 6)



Following general procedure II, (±)-2-chloropropionamide (3.0 mmol, 405 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (544 mg, 92% yield) after column chromatography (eluting with DCM/MeOH 96:4).
^{1}H NMR (300 MHz, $CDCl_3$): δ. 7.31 – 7.18 (5H, m, Ph), 6.82 (1H, br. s, N<u>H</u>), 4.42 – 4.35 (3H, m, CH_3C<u>H</u>Cl and NHC<u>H_2</u>Ph), 1.69 (3H, d, *J* = 7.2 Hz, C<u>H_3</u>CHCl).
^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 137.5, 128.8, 127.8, 127.7, 56.0, 43.9, 22.8.
IR(neat): $\bar{\nu}$ (cm^{-1}) = 1651 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_{10}H_{12}ClNONa]^+$: 220.0505. Found: 220.0491.

2.11. *N*-Benzyl-2-methoxyacetamide[111] (Table 7, Entry 7)



Following general procedure II, 2-methoxyacetamide (3.0 mmol, 267 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (469 mg, 87% yield) after column chromatography (eluting with DCM/MeOH 96:4).

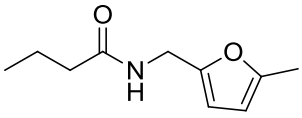
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 – 7.31 (5H, m, Ph), 6.88 (1H, br. s, N<u>H</u>), 4.54 (2H, d, *J* = 5.8 Hz, C<u>H</u>$_2$Ph), 4.00 (2H, s, $CH_3OC\underline{H}_2C(O)$), 3.45 (3H, s, $OC\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 138.1, 128.8, 127.9, 127.6, 72.1, 59.2, 42.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1652 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_{10}H_{14}NO_2H]^+$: 180.1025. Found: 180.1031.

2.12. *N*-(5-Methylfurfuryl)butyramide[16] (Table 7, Entry 8)



Following general procedure II, *n*-butyramide (3.0 mmol, 261 mg) was used as the amide species and 5-methylfurfurylamine (3.6 mmol, 401 µL) as the amine species. The *title compound* was recovered as a dark brown oil (490 mg, 90% yield) after column chromatography (eluting with DCM/MeOH 97:3).

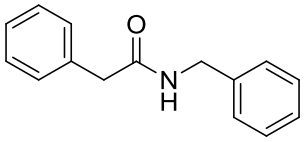
^{1}H NMR (300 MHz, $CDCl_3$): δ. 6.04 – 5.88 (2H, br. m, N<u>H</u> and $CH_3C(O)CHC\underline{H}$), 5.86 (1H, d, *J* = 2.1 Hz, $CH_3C(O)C\underline{H}CH$), 4.34 (2H, d, *J* = 5.4 Hz, $NHC\underline{H}_2C(O)$), 2.23 (3H, s, $CC\underline{H}_3$), 2.15 (2H, t, *J* = 7.5 Hz, $CH_3CH_2C\underline{H}_2$), 1.65 (2H, sext, *J* = 7.5 Hz, $CH_3C\underline{H}_2CH_2$), 0.92 (3H, t, *J* = 7.5 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 151.8, 149.6, 108.1, 106.2, 38.5, 36.5, 19.1, 13.7, 13.5.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1643 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{10}H_{15}NO_2H]^+$: 182.1181. Found: 182.1188.

2.13. *N*-Benzyl-2-phenylacetamide[21] (Table 7, Entry 9)



Following general procedure II, 2-phenylacetamide (3.0 mmol, 405 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (567 mg, 84% yield) after column chromatography (eluting with DCM/MeOH 98:2).

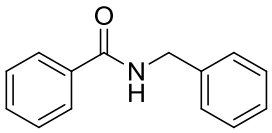
^{1}H NMR (250 MHz, $CDCl_3$): δ 7.38 – 7.17 (10H, m, 2 x Ph), 5.75 (1H, br. s, NH), 4.42 (2H, d, *J* = 5.8 Hz, NHCH_2Ph), 3.63 (2H, s, PhCH_2CO).

^{13}C NMR (63 MHz, $CDCl_3$): δ 170.9, 138.2, 134.8, 129.5, 129.1, 128.7, 127.5, 127.4, 43.8, 43.6.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1636 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{15}H_{14}NO]^-$: 224.1075. Found: 224.1076.

2.14. *N*-Benzylbenzamide[107] (Table 7, Entry 10)



Following general procedure II, benzamide (3.0 mmol, 363 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (590 mg, 93% yield) after column chromatography (eluting with DCM/MeOH 98:2).

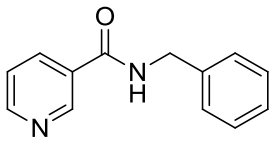
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 – 7.71 (2H, m, 2 x Ar CH), 7.18 – 7.45 (8H, m, 8 x Ar CH), 6.39 (1H, br. s, NH), 4.56 (2H, d, *J* = 5.7 Hz, NHCH_2Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.5, 138.3, 134.4, 131.5, 128.8, 128.6, 127.9, 127.6, 127.0, 44.1.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1637 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{14}H_{13}NOH]^+$: 212.1075. Found: 212.1088.

2.15 *N*-Benzylnicotinamide[112] (Table 7, Entry 11)



Following general procedure II, nicotinamide (3 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) was used as the amine species. After removing the solvent the crude reaction mixture was partitioned between DCM and $NaHCO_3$ before the organics were washed as with general procedure II. The *title compound* was recovered as an off white solid (535 mg, 84% yield) after column chromatography (eluting with DCM/MeOH 90:10).

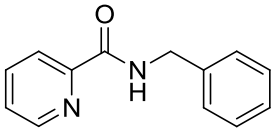
^{1}H NMR (300 MHz, d6-DMSO): δ 9.28 (1H, br. s, NH), 9.10 (1H, d, *J* = 1.6 Hz, Pyridine CH), 8.75 (1H, dd, *J* = 4.8, 1.6 Hz, Pyridine CH), 8. 35 – 8.19 (1H, m, Pyridine CH), 7.54 (1H, ddd, *J* = 7.9, 4.8, 0.7 Hz, Pyridine CH), 7.43 – 7.20 (5H, m, Ph), 4.55 (2H, d, *J* = 6.0 Hz, NHCH_2Ph).

^{13}C NMR (75 MHz, d6-DMSO): δ 165.2, 152.3, 148.8, 139.7, 135.4, 130.2, 128.7, 127.6, 127.2, 123.8, 43.0.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1633 (C=O stretch).

HMRS(ESI-TOF) calcd for $[C_{13}H_{12}N_2ONa]^+$: 235.0847. Found: 235.0861.

2.16. *N*-Benzylpicolinamide[113] (Table 7, Entry 12)



Following general procedure II, picolinamide (3 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) was used as the amine species. After removing the solvent the crude reaction mixture was partitioned between DCM and $NaHCO_3$ before the organics were washed as with general procedure II. The *title compound* was recovered as an off-white solid (548 mg, 86% yield) after column chromatography (eluting with DCM/MeOH 90:10).

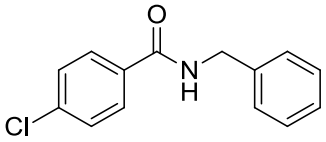
^{1}H NMR (300 MHz, d6-DMSO): δ 9.31 (1H, t, *J* = 5.8 Hz, NH) 8.65 – 8.62 (1H, ddd, *J* = 4.7, 1.5, 0.9, Pyridine CH), 8.07 – 7.95 (2H, m, 2 x Pyridine CH), 7.55 – 7.61 (1H, m, Pyridine CH), 7.34 – 7.18 (5H, m, Ph), 4.50 (2H, d, *J* = 6.4 Hz, NHCH_2Ph).

^{13}C NMR (75 MHz, d6-DMSO): δ 164.3, 150.4, 148.8, 139.9, 138.2, 128.6, 127.7, 127.1, 126.9, 122.3, 42.8.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1658 (C=O stretch).

HMRS(ESI-TOF) calcd for $[C_{13}H_{12}N_2OH]^+$: 213.1028. Found: 213.1042.

2.17. *N*-Benzyl-4-chlorobenzamide[16] (Table 7, Entry 13)



Following general procedure II, 4-chlorobenzamide (3.0 mmol, 363 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white crystalline solid (560 mg, 76% yield) after column chromatography (eluting with DCM/MeOH 98:2).

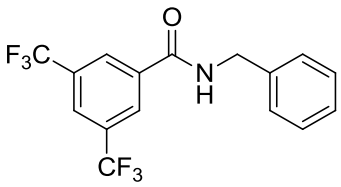
^{1}H NMR (300 MHz, d6-DMSO): δ 9.11 (1H, t, *J* = 5.8 Hz, NH), 7.97 – 7.81 (2H, m, 2 x Aryl CH), 7.60 – 7.43 (2H, m, 2 x Aryl CH), 7.35 – 7.07 (5H, m, Ph), 4.48 (2H, d, *J* = 6.0 Hz, NHCH_2Ph).

^{13}C NMR (75 MHz, d6-DMSO): δ 165.5, 139.8, 136.4, 133.4, 129.6, 128.8, 128.7, 127.6, 127.1, 43.1.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1637 (C=O stretch).

HMRS(ESI-TOF) calcd for $[C_{14}H_{11}ClNOH]^+$: 246.0686. Found: 246.0694.

2.18. *N*-Benzyl-3,5-bis(trifluoromethyl)benzamide[114] (Table 7, Entry 14)



Following general procedure II, 3,5-bis(trifluoromethyl)benzamide (3.0 mmol, 771 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the

amine species. The *title compound* was recovered as a white crystalline solid (968 mg, 93% yield) after column chromatography (eluting with DCM/EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.28 – 8.19 (2H, m, 2 x Aryl C<u>H</u>), 8.00 (1H, s, 1 x Aryl C<u>H</u>), 7.43 – 7.27 (5H, m, Ph), 6.66 (1H, br. s, N<u>H</u>), 4.66 (2H, d, *J* = 5.6 Hz, C<u>H</u>$_2$Ph).

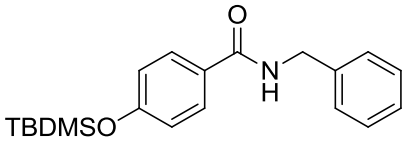
^{13}C NMR (75 MHz, medium acquisition time, $CDCl_3$): δ 164.5, 137.3, 136.3, 132.2 (q, $^{2}J_{CF}$ = 34.0 Hz), 129.0, 128.1, 128.0, 127.4 (q, $^{3}J_{CF}$ = 3.5 Hz), 125.1 (app. sept., $^{3}J_{CF}$ = 3.5 Hz), 122.9 (q, $^{1}J_{CF}$ = 273.4 Hz), 44.6.

^{19}F (376 MHz, $CDCl_3$): δ -62.86.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1642 (C=O stretch)

HMRS(ESI-TOF) calcd for $[C_{16}H_{11}F_6NONa]^+$: 370.0642. Found: 370.0660.

2.19. *N*-Benzyl-4-((tert-butyldimethylsilyl)oxy)benzamide (Table 7, Entry 15)



Following general procedure II, 4-((tert-butyldimethylsilyl)oxy)benzamide (3.0 mmol, 754 mg,) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (748 mg, 73% yield) after column chromatography (eluting with DCM/EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 – 7.60 (2H, m, 2 x Aryl C<u>H</u>), 7.40 – 7.23 (5H, m, Ph) 6.92 – 6.79 (2H, m, 2 x Aryl C<u>H</u>), 6.32 (1H, br. s, N<u>H</u>), 4.63 (2H, d, *J* = 5.7 Hz, NHC<u>H</u>$_2$Ph), 0.98 (9H, s, *t*Bu), 0.21 (6H, s, 2 x C<u>H</u>$_3$).

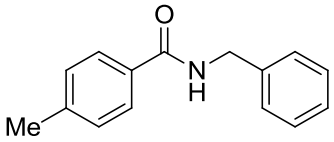
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 158.8, 138.4, 128.8, 128.7, 128.0, 127.6, 120.1, 44.1, 25.6, 18.3, -4.4.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1636 (C=O stretch).

HMRS(ESI-TOF) calcd for $[C_{20}H_{27}CNO_2SiNa]^+$: 364.1709. Found: 364.1702.

Melting Point: 113-114 °C

2.20. *N*-Benzyl-4-methylbenzamide[115] (Table 7, Entry 16)



Following general procedure II, 4-methylbenzamide (3.0 mmol, 405 mg) was used as the amide species and benzylamine (393 µL, 3.6 mmol) as the amine species. The *title compound* was recovered as a white crystalline solid (446 mg, 66% yield) after column chromatography (eluting with DCM/MeOH 98:2).

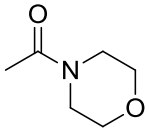
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 – 7.63 (2H, m, 2 x Aryl C<u>H</u>), 7.39 – 7.16 (7H, m, 2 x Aryl C<u>H</u> and Ph), 6.41 (1H, br. s, N<u>H</u>), 4.64 (2H, d, *J* = 5.7 Hz), 2.39 (3H, s, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 142.1, 138.5, 131.7, 129.4, 128.9, 128.1, 127.7, 127.1, 44.2, 21.5.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1638 (C=O stretch).

HMRS(ESI-TOF) calcd for $[C_{15}H_{16}NOH]^{+}$: 226.1232. Found: 226.1226.

2.22. 1-Morpholinoethanone[108] (Table 7, Entry 18)



Following general procedure II, acetamide (3 mmol, 177 mg) was used as the amide species and morpholine (3.6 mmol, 301 µL). The *title compound* was recovered as a as a light brown oil (333 mg, 86% yield) after column chromatography (eluting with DCM/MeOH 96:4)

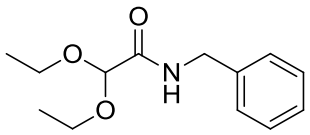
^{1}H NMR (250 MHz, $CDCl_3$) δ 3.61 - 3.53 (6H, m, 2 x NC<u>H</u>C<u>H</u>$_2$O), 3.42- 3.38 (2H, m, 2 x NC<u>H</u>CH_2), 2.02 (3H, s, C<u>H</u>$_3$C(O)N).

^{13}C NMR (63 MHz, $CDCl_3$) δ 169.1, 66.7, 66.5, 46.6, 41.7, 21.1.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1606 (C=O stretch).

HMRS(ESI-TOF) calcd for $[C_6H_{11}NO_2Na]^{+}$: 152.0687 . Found: 152.0692.

2.23. *N*-Benzyl-2,2-diethoxyacetamide[116] (Table 7, Entry 19)



Following general procedure II, 2,2-diethoxyacetamide (3 mmol, 439 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) was used as the amine species. The *title compound* was recovered as an light brown oil (598 mg, 84% yield) after column chromatography eluting with 1:1 Hex : EtOAc.

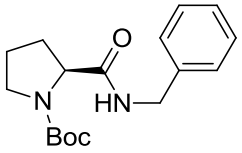
^{1}H NMR (300 MHz,$CDCl_3$): δ 7.36 – 7.24 (5H, m, Ph), 6.92 (1H, br. s, NH), 4.85 (1H, s, $O_2CHC(O)$), 4.47 (2H, d, *J* = 6.0 Hz, $NHCH_2Ph$), 3.74 – 3.56 (4H, m, 2 x CH_3CH_2O), 1.23 (6H, t, *J* = 7.5 Hz, 2 x CH_3CH_2O).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 137.9, 128.7, 127.8, 127.6, 98.5, 62.6, 43.0, 15.1.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1673 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{13}H_{18}NO_3]^-$: 236.1287. Found: 236.1294.

2.24. [*N*-(Benzyl)-*N'*-Boc]-L-prolinamide[117] (Table 7, Entry 20)



Following general procedure II, *N*-Boc-L-prolinamide (2 mmol, 439 mg) was used as the amide species and benzylamine (2.4 mmol, 262 µL) was used as the amine species. The *title compound* was recovered as a white solid (445 mg, 73% yield) after column chromatography (eluting with Hex/EtOAc 1:1). The product was observed as two rotamers in its NMR spectra.

^{1}H NMR (300 MHz, d6-DMSO): δ 8.40 – 8.32 (1H, m, NH), 7.33 – 7.21 (5H, m, Ph), 4.38 – 4.07 (3H, m, pyrrolidine ring and $NHCH_2Ph$), 3.44 – 3.25 (1H, m, pyrrolidine ring), 1.86 – 1.72 (3H, m, pyrrolidine ring), 1.43 (9H, s, (minor rotamer), *t*Bu), 1.29 (9H, s, (major rotamer), *t*Bu).

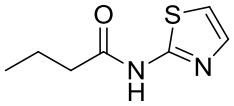
^{13}C NMR (75 MHz, d6-DMSO): δ 172.8, 172.6, 154.1, 153.7, 140.0, 128.5, 127.7, 127.2, 127.1, 126.9, 79.0, 78.8, 60.3, 60.2, 47.0, 46.8, 42.4, 42.2, 31.5, 30.4, 28.5, 28.3, 24.3, 23.5.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1682 (C=O stretch, Boc group), 1653 (C=O stretch amide)

HRMS (ESI-TOF) calcd for $[C_{17}H_{24}N_2O_3H]^+$: 305.1865. Found: 305.1853.

$[\alpha]_D^{25}$ = -80.0 ($CHCl_3$, *c* = 1.0), literature value $[\alpha]_D^{25}$ = -80.2°; *ee* >99%, Chiracel AD column (25 cm) with AD pre-column (5 cm), 0.5 mL min^{-1}, 90:10 Hex/IPA, (*L*) enantiomer retention time 25.11 min, (*D*) enantiomer retention time 16.68 min.

2.25. *N*-(Thiazol-2-yl)butyramide[118] (Table 7, Entry 21)



Following general procedure II, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 2-aminothiazole (3.6 mmol, 361 mg) as the amine species. The *title compound* was recovered as beige solid (347 mg, 68% yield) after column chromatography (eluting with Hex/EtOAc 1:1)

^{1}H NMR (300 MHz, d6-DMSO): δ 12.02 (1H, s, NH), 7.45 (1H, d, *J* = 3.6 Hz, SCHCHN), 7.16 (1H, d, *J* = 3.6 Hz, SCHCHN), 2.40 (2H, t, *J* = 7.3 Hz, $CH_2CH_2C(O)$), 1.59 (2H, sext, *J* = 7.4 Hz, $CH_3CH_2CH_2$), 0.89 (3H, t, *J* = 7.4 Hz, CH_3CH_2).

^{13}C NMR (75 MHz, d6-DMSO): δ 171.4, 158.4, 137.9, 113.5, 37.1, 18.5, 13.9.

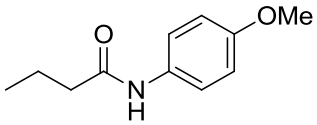
HRMS(ESI-TOF) calcd for $[C_7H_{10}N_2OSNa]^+$: 193.0412 . Found: 193.0421.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1686 (C=O stretch).

Anal. Calcd for $C_7H_{10}N_2OS$: C, 49.39; H, 5.92; N, 16.46 Found: C, 49.40; H, 5.92; N, 16.40.

Melting Point: 133-134 °C (lit.: 132-134 °C)

2.26. 4-(Methoxyphenyl)butyramide[119] (Table 7, Entry 22)



Following general procedure II, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 4-methoxyaniline (3.6 mmol, 443 mg) was used as the amine species. The *title compound* was recovered as a light pink solid (313 mg, 54% yield) after column chromatography (eluting with 1:1 Hex/EtOAc) and multiple recrystallisation from DCM-Hex.

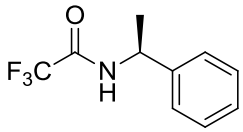
^{1}H NMR (300 MHz,$CDCl_3$): δ 7.41 (2H, d, *J* = 9 Hz, 2 x Aryl CH), 7.31 (1H, br. s, N<u>H</u>), 6.84 (2H, d, *J* = 9 Hz, 2 x Aryl CH), 3.78 (3H, s, O<u>CH</u>$_3$), 2.31 (2H, t, *J* = 7.5 Hz, CH_2<u>CH_2</u>C(O)), 1.75 (2H, sext., *J* = 7.5 Hz, CH_3<u>CH_2</u>CH_2), 0.99 (3H, t, *J* = 7.3 Hz, <u>CH_3</u>CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 156.4, 131.1, 121.8, 114.1, 55.5, 39.5, 19.2, 13.8.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1648 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{11}H_{14}NO_2]^-$: 192.1025. Found: 192.1036.

2.26. (S)-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide[120] (Table 8, Entry 1)



Following general procedure II, 2,2,2-trifluoroacetamide (3.0 mmol, 339 mg) was used as the amide species and (*S*)-(−)-α-methylbenzylamine (3.6 mmol, 464 μL) as the amine species. The *title compound* was recovered as a white crystalline solid (573 mg, 88% yield) after column chromatography (eluting with DCM/MeOH 98:2).

^{1}H NMR (300 MHz, d6-DMSO): δ 9.85 (1H, d, *J* = 7.6 Hz, N<u>H</u>), 7.54 – 7.00 (5H, m, Ph), 5.00 (1H, app. quin., *J* = 7.2 Hz, NHC<u>H</u>Ph), 1.45 (3H, d, *J* = 7.1 Hz, <u>CH_3</u>CH).

^{13}C NMR (75 MHz, d6-DMSO): δ 155.8 (q, J_{CF} = 36.8 Hz), 143.2, 128.8, 127.5, 126.4, 116.2 (q, J_{CF} = 287.3 Hz), 49.4, 21.7.

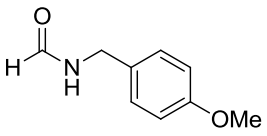
^{19}F (376 MHz, d6-DMSO): δ -74.09.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1698 (C=O stretch).

HMRS (ESI-TOF) calcd for $[C_{10}H_9F_3NO]^-$: 216.0636. Found: 216.0663.

$[\alpha]_D^{25}$ = -137.0 ($CHCl_3$, *c* = 1.0), literature value for (*R*) enantiomer $[\alpha]_D^{25}$ = +137°;[120] *ee* > 99%, Chiracel OD-H column (25 cm), 1.3 mL min^{-1}, 98:2 Hex/IPA, (S) enantiomer retention time 11.09 min, (R) enantiomer retention time 18.15 min.

2.27. *N*-(4-Methoxybenzyl)formamide[41] (Table 8, Entry 2)



Following general procedure II, formamide (3.0 mmol, 120 µL) was used as the amide species and 4-methoxybenzylamine (3.6 mmol, 470 µL) as the amine species. The *title compound* was recovered as a white solid (446 mg, 90% yield) after column chromatography (eluting with DCM/MeOH 96:4). The product was observed as two rotamers in its NMR spectra.

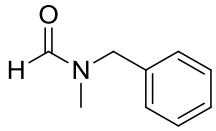
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (1H, s, (major rotamer), HC(O)NH), 8.14 (1H d, (minor rotamer), *J* = 12 Hz, HC(O)NH), 7.23 – 7.14 (2H, m, (major and minor rotamer), 2 x CH Ar), 6.90 – 6.83 (2H, m, (major and minor rotamer), 2 x CH Ar), 6.00 (1H, br. s, NH), 4.39 (2H, d, (major rotamer), *J* = 6.0 Hz, $NHCH_2Ph$), 4.33 (2H, d, (minor rotamer), *J* = 6.0 Hz, $NHCH_2Ph$), 3.80 (3H, s, (minor rotamer), OCH_3), 3.78 (3H, s, (major rotamer), OCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5 (minor rotamer), 161.0 (major rotamer), 159.2, 129.7 (major rotamer), 129.5 (minor rotamer), 129.2 (major rotamer), 128.3 (minor rotamer), 114.3 (minor rotamer), 114.2 (major rotamer), 55.3, 45.2 (minor rotamer), 41.7 (major rotamer).

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1660 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_9H_{11}NO_2H]^+$: 166.0868. Found: 166.0879.

2.28. *N*-Benzyl-*N*-methylformamide[41] (Table 8, Entry 3)



Following general procedure II, formamide (3.0 mmol, 120 µL) was used as the amide species and *N*-benzylmethylamine (3.6 mmol, 465 µL) as the amine species. The *title compound* was recovered as an orange-brown oil (425 mg, 95% yield) after

column chromatography (eluting with DCM/MeOH 96:4). The product was observed as two rotamers in its NMR spectra.

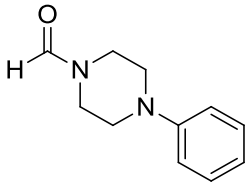
^{1}H NMR (300 MHz, $CDCl_3$): δ. 8.17 (1H, s, (major rotamer), HC(O)NH), 8.04 (1H (minor rotamer), s, HC(O)NH), 7.29 - 7.07 (5H, m), 4.41 (2H, s, (minor rotamer), $N(CH_3)CH_2Ph$), 4.27 (2H, s, (major rotamer), $N(CH_3)CH_2Ph$), 2.73 (3H, s, (minor rotamer), NCH_3), 2.66 (3H, s, (major rotamer), NCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7 (major rotamer), 162.6 (minor rotamer), 136.1 (minor rotamer), 135.8 (major rotamer), 128.9 (major rotamer), 128.7 (minor rotamer), 128.2 (major rotamer), 128.1 (minor rotamer), 127.6 (minor rotamer), 127.4 (major rotamer), 53.4 (major rotamer), 47.7 (minor rotamer), 34.0 (major rotamer), 29.4 (minor rotamer).

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1659 (C=O stretch).

HRMS (ESI-TOF) calcd for $[C_9H_{11}NONa]^+$: 172.0738. Found: 172.0742.

2.29. Phenylpiperazine-1-carbaldehyde[121] (Table 8, Entry 4)



Following general procedure II, formamide (3 mmol, 120 µL) was used as the amide species and 1-phenylpiperizine (3.6 mmol, 549 µL) was used as the amine species. The *title compound* was recovered as a beige solid (507 mg, 89% yield) after column chromatography (eluting with 90:10 DCM:MeOH).

^{1}H NMR (300 MHz,$CDCl_3$): δ 8.04 (1H, s, HC(O)NH), 7.26 – 7.19 (2H, m, Ph), 6.91 – 6.85 (3H, m, Ph), 3.66 (2H, t, *J* = 5.4 Hz, $C(O)NCH_2CH_2$), 3.48 (2H, t, *J* = 5.4 Hz, $C(O)NCH_2CH_2$), 3.08-3.15 (4H, m, 2 x CH_2CH_2NPh).

^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 129.4, 121.2, 117.3, 50.7, 49.6, 45.5, 39.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1650 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{11}H_{14}N_2OH]^+$: 191.1184. Found: 191.1176.

Use of Secondary and Tertiary Amides (Chapter 2 Section 2.5.3.)

As with general procedure II, *N*-methylacetamide (76 µL, 1 mmol), DMAC (93 µL, 1 mmol) or 4'-methylacetanilide (149 mg, 1 mmol) were used as the amide species and benzylamine (131 µL, 1.2 mmol) as the amine species. After 18 hours, solvent was removed *in vacuo* and the crude conversions were determined by analysis of crude ^{1}H NMR spectra.

Use of Sulfonamides and Phosphinamides (Chapter 2 Section 2.5.4.)

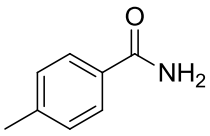
As with general procedure II, *p*-toluenesulfonamide (171 mg, 1 mmol) or diphenylphosphinamide (217 mg, 1 mmol) were used as the amide species and benzylamine (131 µL, 1.2 mmol) as the amine species. After 18 hours, solvent was removed *in vacuo* and the crude conversions were determined by analysis of crude ^{1}H NMR spectra.

Reversibility Studies (Chapter 2, Section 2.6.1.)

As with general procedure II, in one reaction *N*-allylbutyramide **2.06** (127 mg, 1 mmol) was used as the amide species and benzylamine (109 µL, 1.0 mmol) as the amine species. In another reaction *N*-benzylbutyramide **2.03** (177 mg, 1 mmol) was used as the amide species and allylamine (75 µL, 1.0 mmol) as the amine species. After 18 hours, the solvent was removed *in vacuo* from both reactions and the crude conversions were determined by analysis of crude ^{1}H NMR spectra.

General Procedure III. Ammonia Trapping Procedure: Following general procedure II, butyramide (3.0 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. Into this sealed Radley's carousel tube a cannula was added from the vessel headspace across into the solution of a separate stoppered 100 mL round bottom flask. Within which was 1,4-dioxane (15 mL), *p*-tolyl chloride (3 mmol, 397 µL) and triethylamine (3.6 mmol, 448µL). A slight positive pressure of nitrogen was created by connecting the side arm of the Radley's carousel tube and opening the tap. After 5 hours the solvents of each reaction were removed *in vacuo* and the *p*-tolyl chloride reaction, (Scheme 46, *Reaction 2*) worked up as with general procedure II.

2.35. *p*-Toluamide[122]



Following general procedure III, *title compound* was isolated a fluffy white solid (154 mg, 38% yield) by recrystallisation from DCM/Hex.

^{1}H NMR (300 MHz, d6-DMSO): δ 7.89 (1H, br. s NH), 7.78 (2H, d, *J* = 8.2 Hz, 2 x Ar CH), 7.35 – 7.20 (3H, m, 2 x Ar CH and NH), 2.34 (3H, s, ArCH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 168.2, 141.4, 131.8, 129.1, 127.9, 21.3.

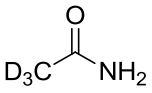
IR(neat): $\bar{\nu}$ (cm^{-1}) = 1667 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_8H_9NOH]^+$: 136.0762. Found: 136.0769.

General Procedure IV. Preparation of primary amides *via* nitrile hydration:

Based on a modified literature procedure,[88] chlorotrimethylsilane (two equivalents) was added to the stirring nitrile which was cooled to 0 °C in an ice bath. To this deionised H_2O (three equivalents) was added dropwise, after which the reaction was allowed to come to room temperature and left stirring for 4 hours. A gelatinous precipitate was noted to form at the bottom of the reaction mixture. The reaction mixture cooled in an ice bath and was neutralised using a sat. $NaHCO_3$ (approx. 25 mL) and the aqueous was extracted using EtOAc (3 x 150 mL). The organics were dried using $MgSO_4$, filtered and evaporated to dryness, giving the *title* amide.

2.39. **2,2,2-Trideuteroacetamide[123]** (Chapter 2 Section 2.6.3)



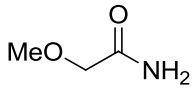
Following general procedure IV,d_3-MeCN (47.9 mmol, 2.5 mL, >99.5% in D) was used as the nitrile species, to this was added chlorotrimethylsilane (96 mmol, 12.24 mL) followed by dropwise addition of deionised H_2O (144 mmol, 2.59 mL). The *title* compound was isolated, after evaporation of the organics, as a white fluffy solid (594 mg, 20% yield).

^{1}H NMR (250 MHz, d6-DMSO): 7.21 (1H, br. s), 6.62 (1H, br. s).

^{13}C NMR (500 MHz, d6-DMSO): 172.0, 22.5-21.9 (m, $J_{C\text{-}D}$).

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1635 (C=O stretch)

2-Methoxyacetamide[124]



Following general procedure IV, methoxyacetonitrile (67.2 mmol, 5 mL) was used as the nitrile species, to this was added Me_3SiCl (134.48 mmol, 17.07 mL) followed by deionised H_2O (201.7 mmol, 3.6 mL) was added dropwise. The *title* compound was isolated, after evaporation of the organics, as a white solid (1.199 g, 20% yield).

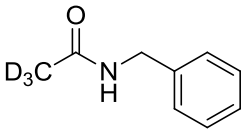
^{1}H NMR (300 MHz, $CDCl_3$): 6.50 (2H, br. s, N$\underline{H}_2$), 3.85 (2H, s, C$\underline{H}_2$OCH$_3$), 3.39 (3H, s, OC$\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$): 173.0, 71.7, 59.2.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1630 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_3H_7NO_2Na]^+$: 112.0374. Found: 112.0385.

***N*-Acylation of benzylamine using 2,2,2-trideuteroacetamide**[125] (Chapter 2, Section 2.6.3)



As with general procedure II, 2,2,2-trideuteroacetamide (124 mg, 2 mmol) was used as the amide species and benzylamine (314 µL, 2.4 mmol) as the amine species. Analysis of the product **2.40** after workup and column chromatography showed an 89/11 (D/H) incorporation at the α-position.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 – 7.20 (5H, m, Ph), 5.92 (1H, br. s, N$\underline{H}$), 4.41 (2H, d, *J* = 5.7 Hz, NHC$\underline{H}_2$Ph)

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 138.2, 128.7, 127.9, 127.6, 43.7.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1625.61 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_{11}H_{15}NONa]^+$: (M+3) 175.0927 Found: 175.0938

5.3 Chapter 3 Experimental Methods and Compound Characterisation

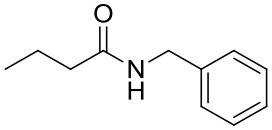
General Procedure V. Enhanced transamidation with the use of base (Chapter 3, Section 3.2.1.):
Butyramide (87 mg, 1 mmol) was added to an oven dried Radleys carousel tube with a magnetic stirrer and the tube was sealed and purged with N_2. After 10 minutes anhydrous cyclohexane (1 mL) was added to the tube and the tube was cooled to 0 °C. To this was added the appropriate base (10 mol%, see **Table 11**), after this the reaction was stirred for 0.5 hours at room temperature. Following this zirconocene dichloride (0.05 mmol, 5 mol%) was added and the reaction left for a further 0.5 hours at this temperature. Subsequently, benzylamine (131 µL, 1.2 mmol) was added and the reaction heated to 40 °C for 5 hours. After this the solvent was removed *in situ* and conversions were determined by analysis of the crude ^{1}H NMR spectra.

General Procedure VI. Catalytic Additive Screen and Optimisation (Chapter 3, Section 3.2): Zirconocene dichloride (0.05 mmol, 5 mol%) and the appropriate catalytic additive (0.10 mmol, 10 mol%), if additive was a solid, was added to an oven dried Radleys carousel tube with a magnetic stirrer and the tube was sealed and purged with N_2. After 10 minutes anhydrous cyclohexane (1 ml) was added to the tube, followed by the catalytic additive (0.10 mmol, 10 mol%), if it was a liquid. The reaction was then heated with stirring at 40 ^{o}C for 1 hour. *n*-Butyramide (87 mg, 1 mmol) and benzylamine (131 µL, 1.2 mmol) were added and the tube re-sealed and heated at 40 ^{o}C for between 5-24 hours. After which the reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* and the crude reaction mixtures were analysed by their ^{1}H NMR spectra

General Procedure VII. *N*-Acylation of Amines with Amides (Chapter 3, Section 3.3.): An oven dried Radleys carousel tube was charged with amide species (one equivalent) and zirconocene dichloride (5 mol%) and the tube was sealed and purged with N_2 for around 10 minutes. After which anhydrous cyclohexane, volume as appropriate, was added followed by (trimethysilyl)isothiocyanate (10 mol%) The reaction was then heated with stirring at either 40 or 80 ^{o}C (see **Table 16**) for 1 hour. After this, the amine (1.2 equivalents) was added and the tube was heated at 40 or

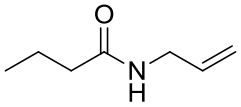
80 ^{o}C for the appropriate time (see **Table 16**). After being allowed to cool to room temperature 5 mL of MeOH was added and the solvent was removed *in vacuo* and the crude reaction mixture was the analysed by ^{1}H NMR and ^{13}C NMR spectroscopy. Unless otherwise stated, dichloromethane (50 mL) was added and the organics washed with water (20 mL). The organics were separated and the aqueous washed with dichloromethane (2 x 50 mL), the organics were combined and dried over $NaSO_4$. Volatiles were removed *in vacuo* and the crude reaction mixture was purified by column chromatography and recrystallisation was carried out as necessary.

2.03. *N*-Benzylbutyramide[126] (Table 16, entry 1)



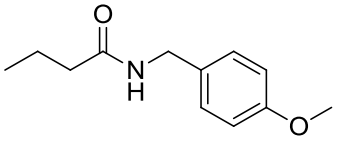
Following general procedure VII, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (473 mg, 89% yield) after column chromatography (eluting with DCM/MeOH 95:5). Analytical data was consistent with that above.

2.06. *N*-Allylbutyramide[16](Table 16, entry 2)



Following general procedure VII, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and allylamine (3.6 mmol, 270 µL) as the amine species. The *title compound* was recovered as a dark orange oil (336 mg, 88% yield) after column chromatography (eluting with DCM/MeOH 95:5). Analytical data was consistent with that above.

3.01. *N*-(4-Methoxybenzyl)butyramide[126] (Table 16, entry 3)



Following general procedure VII *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 4-methoxybenzylamine (3.6 mmol, 469 µL) as the amine species. The *title compound* was recovered as a white solid (535 mg, 86% yield) after column chromatography (eluting with DCM/MeOH 95:5).

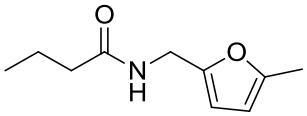
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (2H, dt, *J* = 7.5, 3 Hz, 2 x Aryl C<u>H</u>), 6.85 (2H, dt, *J* = 7.5, 3 Hz, 2 x Aryl C<u>H</u>), 5.88 (1H, br. s, N<u>H</u>), 4.36 (2H, d, *J* = 5.4 Hz, NHC<u>H</u>$_2$Ar), 3.79 (3H, s, OC<u>H</u>$_3$), 2.18 (2H, t, *J* = 7.5 Hz, CH_3CH_2C<u>H</u>$_2$), 1.67 (2H, sext., *J* = 7.5 Hz, CH_3C<u>H</u>$_2CH_2$), 0.94 (3H, t, *J* = 7.4 Hz, C<u>H</u>$_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 159.0, 130.4, 129.2, 114.1, 55.3, 43.1, 38.6, 19.2, 13.8.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1631 (C=O stretch)

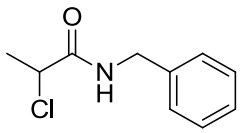
HRMS(ESI-TOF) calcd for $[C_{12}H_{17}NO_2H]^+$: 208.1338. Found: 208.1337

2.12.*N*-(5-Methylfurfuryl)butyramide[16] (Table 16, entry 4)



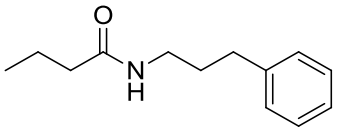
Following general procedure VII, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 5-methylfurfurylamine (3.6 mmol, 401 µL) as the amine species. The *title compound* was recovered as a brown oil (502 mg, 92% yield) after column chromatography (eluting with DCM/MeOH 97:3). Analytical data was consistent with that above.

2.10. (±)-*N*-Benzyl-2-chloropropionamide[110] (Table 16, entry 5)



Following general procedure VII, (±)-2-chloropropionamide (3 mmol, 323 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a pale yellow solid (510 mg, 86% yield) after column chromatography (eluting with DCM/MeOH 96:4). Analytical data was consistent with that above.

3.02. *N*-(3-Phenylpropyl)butyramide[107] (Table 16, entry 6)



Following general procedure VII, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 3-phenylpropylamine (3.6 mmol, 511 µL) as the amine species. The *title compound* was recovered as a light brown oil (468 mg, 76% yield) after column chromatography (eluting with Pet. Ether/Et_2O 1:3).

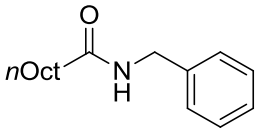
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 – 7.15 (5H, m, Ph), 5.78 (1H, br. s, NH), 3.27 (2H, q, *J* = 6.0 Hz, $NHCH_2CH_2$), 2.63 (2H, t, *J* = 7.5 Hz, CH_2Ph), 2.10 (2H, t, *J* = 7.5 Hz, $CH_2CH_2C(O)$), 1.82 (2H, quin., *J* = 7.5 Hz, $NHCH_2CH_2$), 1.62 (2H, sext., *J* = 7.2 Hz, $CH_2CH_2C(O)$), 0.92 (3H t, *J* = 7.4 Hz, CH_3CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 141.5, 128.5, 128.4, 126.0, 39.2, 38.7, 33.4, 31.3, 19.2, 13.8.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1640 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{13}H_{19}NOH]^+$: 206.1545. Found: 206.1551.

3.03. *N*-Benzylnonanamide[111] (Table 16, entry 7)



Following general procedure VII, *n*-nonanamide (2 mmol, 315 mg) was used as the amide species and benzylamine (2.4 mmol, 262 µL) as the amine species. The *title compound* was recovered as a white solid (397 mg, 80% yield) after column chromatography (eluting with Hex/EtOAc 1:1).

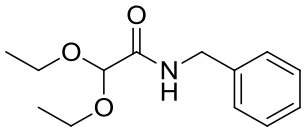
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.25 (5H, m, Ph), 5.77 (1H, br. s, NH), 4.44 (2H, d, *J* = 5.7 Hz, CH_2Ph), 2.20 (2H, t, *J* = 7.5 Hz, $CH_2CH_2C(O)$), 1.70 – 1.60 (2H, m, $CH_2CH_2C(O)$), 1.34 – 1.26 (10H, m, 5 x alkyl CH_2), 0.87 (3H, t, *J* = 6.8 Hz, CH_3CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.0, 138.4, 128.7, 127.9, 127.5, 43.6, 36.9, 31.8, 29.3, 29.2, 25.8, 22.7, 14.1.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1638 (C=O stretch).

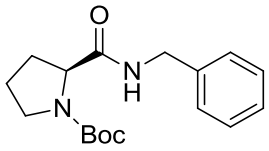
HRMS(ESI-TOF) calcd for $[C_{16}H_{25}NONa]^+$: 270.1834. Found: 270.1836

2.23. *N*-Benzyl-2,2-diethoxyacetamide[116] (Table 16, entry 8)



Following general procedure VII, 2,2-diethoxyacetamide (3 mmol, 442 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a pale brown oil (641 mg, 90% yield) after column chromatography (eluting with EtOAc/Hex 1:1). Analytical data was consistent with that above.

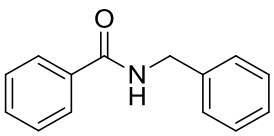
2.24.[*N*-(Benzyl)-*N'*-Boc]-L-prolinamide[117] (Table 16, entry 9)



Following general procedure VII, *N*-Boc-L-prolinamide (2 mmol, 429 mg) was used as the amide species and benzylamine (2.4 mmol, 262 µL) as the amine species. The *title compound* was recovered as a white solid (498 mg, 82% yield) after column chromatography (eluting with EtOAc/Hex 1:1). Analytical data was consistent with that above.

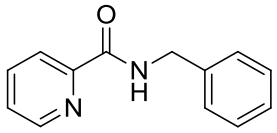
$[\alpha]_D^{25}$ = -80.8 ($CHCl_3$, *c* = 1.0), literature value $[\alpha]_D^{25}$ = -80.2° ($CHCl_3$, *c* = 0.6); Chiracel AD column (25 cm) with AD pre-column (5 cm), 0.5 mL min^{-1}, U.V detector wavelength 238 nm 90:10 Hex/IPA, (*L*) enantiomer retention time 23.48 min, (*D*) enantiomer retention time 16.40 min. Product retention time 24.06 min. *ee* >99%.

2.14. *N*-Benzylbenzamide[111] (Table 16, entry 10)



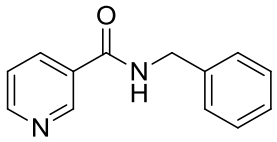
Following general procedure VII, benzamide (3 mmol, 364 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a white solid (520 mg, 82% yield) after column chromatography (eluting with DCM/MeOH 98:2). Analytical data was consistent with that above.

2.16. *N*-Benzylpicolinamide[113] (Table 16, entry 11)



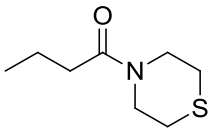
Following general procedure VII, picolinamide (3 mmol, 366 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as an off white solid (581 mg, 91% yield) after column chromatography (eluting with DCM/MeOH 90:10). Analytical data was consistent with that above.

2.15 *N*-Benzylnicotinamide[112] (Table 16, entry 12)



Following general procedure VII, nicotinamide (3 mmol, 366 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as an off white solid (545 mg, 86% yield) after column chromatography (eluting with DCM/MeOH 90:10). Analytical data was consistent with that above.

3.04. 1-Thiomorpholinobutan-1-one[127] (Table 16, entry 13)



Following general procedure VII, butyramide (3 mmol, 261 mg) was used as the amide species and benzylamine (3.6 mmol, 362 µL) as the amine species. The *title compound* was recovered as a colourless oil (444 mg, 85% yield) after column chromatography (eluting with EtOAc/Hex 1:1).

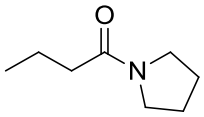
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 – 3.82 (2H, m, $NC\underline{H_2}CH_2$), 3.71 – 3.68 (2H, m, 2 x $NC\underline{H_2}CH_2$), 2.60 – 2.52 (4H, m, 2 x $SC\underline{H_2}CH_2$), 2.25 (2H, t, *J* = 7.5 Hz, $CH_2C\underline{H_2}C(O)$), 1.70 – 1.52 (2H, sext., *J* = 7.8 Hz, $CH_3C\underline{H_2}$), 0.92 (3H, t, *J* = 7.4 Hz, $C\underline{H_3}CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 48.3, 44.1, 35.4, 27.9, 27.4, 18.7, 14.0.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1635 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_8H_{15}NOSNa]^+$: 196.0772. Found: 196.0776

3.05 1-(Pyrrolidin-1-yl)butan-1-one[126] (Table 16, entry 14)



Following general procedure VII, butyramide (3 mmol, 261 mg) was used as the amide species and pyrrolidine (3.6 mmol, 301 µL) as the amine species. The *title compound* was recovered as a yellow oil (341 mg, 80% yield) after column chromatography (eluting with EtOAc/DCM 1:1).

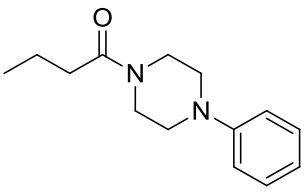
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 – 3.32 (4H, m, 2 x $NC\underline{H_2}CH_2$), 2.17 (2H, t, *J* = 7.5 Hz), 1.92 – 1.73 (4H, m, 2 x $NCH_2C\underline{H_2}$), 1.60 (2H, sext, *J* = 7.2 Hz, $CH_2C\underline{H_2}C(O)$), 0.89 (3H, t, *J* = 7.4 Hz, $C\underline{H_3}CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 46.6, 45.5, 36.7, 26.1, 24.4, 18.3, 14.0.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1622 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_8H_{15}NOH]^+$: 142.1232. Found: 142.1264

3.06. 1-(4-Phenylpiperazin-1-yl)butan-1-one (Table 16, entry 15)



Following general procedure VII, butyramide (3 mmol, 261 mg) was used as the amide species and 1-phenylpiperazine (3.6 mmol, 550 µL) as the amine species. The *title compound* was recovered as a white solid (564 mg, 81% yield) after column chromatography (eluting with EtOAc/DCM 1:1) and recrystallisation from DCM-Pentane.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.25 (2H, m, 2 x Aryl CH), 6.95 – 6.88 (3H, m, 2 x Aryl CH), 3.80 – 3.77 (2H, m, C(O)NC$\underline{H}_2$), 3.65 – 3.61 (2H, m, C(O)NC$\underline{H}_2$), 3.16 (4H, dd, *J* = 10.6, 6.7 Hz, 2 x C$\underline{H}_2$NPh), 2.35 (2H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_2C$(O)), 1.69 (2H, sext., *J* = 7.2 Hz, $CH_3C\underline{H}_2$), 0.99 (3H, t, *J* = 7.4 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 151.0, 129.3, 120.6, 116.7, 49.9, 49.5, 45.5, 41.4, 35.3, 18.8, 14.1.

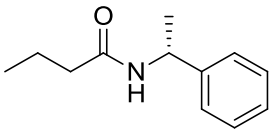
IR(neat): $\bar{\nu}$ (cm^{-1}) = 1630 (C=O stretch).

HRMS(ESI-TOF) calcd for $[C_{14}H_{20}N_2OH]^+$: 233.1654. Found: 233.1655.

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06 Found: C, 72.50; H, 8.57; N, 12.01.

Melting Point: 85-87 ^{o}C (DCM-Pentane).

3.07. (*R*)-*N*-(1-Phenylethyl)butyramide[126] (Table 16, entry 16)



Following general procedure VII, butyramide (3 mmol, 261 mg) was used as the amide species and (*R*)-(+)-α-methylbenzylamine (3.6 mmol, 458 µL) as the amine species. The *title compound* was recovered as a beige solid (425 mg, 74% yield) after column chromatography (eluting with DCM/EtOAc 2:1).

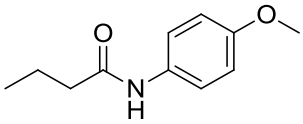
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.09 (5H, m, Ph), 5.76 (1H, s, N$\underline{H}$), 5.17 – 4.90 (1H, m, NHC$\underline{H}$(CH_3)), 2.08 (2H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_2C$(O)), 1.59 (2H, sext., *J* = 7.8 Hz, $CH_3C\underline{H}_2$), 1.41 (3H, d, *J* = 6.9 Hz, (C$\underline{H}_3$)CHNH), 0.86 (t, *J* = 7.4 Hz, 3H, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 143.3, 128.7, 127.3, 126.2, 48.6, 38.7, 21.8, 19.2, 13.7.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1638 (C=O stretch).

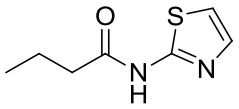
HRMS(ESI-TOF) calcd for $[C_{12}H_{16}NO]^-$:190.1232. Found: 190.1244.
$[\alpha]_D^{25}$ = +119.0° ($CHCl_3$, *c* = 1.0), literature value $[\alpha]_D^{20}$ = +107.0° ($CHCl_3$, *c* = 0.6) Chiracel AD column (25 cm) with AD pre-column (5 cm), 1.0 mL min^{-1}, U.V detector wavelength 254 nm, 95:5 Hex/IPA, (*R*) enantiomer retention time 12.35 min, (*S*) enantiomer retention time 16.48 min. Product retention time 12.90 min. >99% *ee*.

2.26 *N*-(4-Methoxyphenyl)butyramide[119] (Table 16, entry 17)



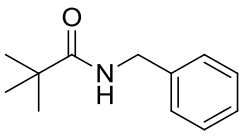
Following general procedure VII, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 4-methoxyaniline (3.6 mmol, 443 mg) as the amine species. The *title compound* was recovered as a light brown solid (457 mg, 79% yield) after column chromatography (eluting with EtOAc/Hex 1:1). Analytical data was consistent with that above.

2.25. *N*-(Thiazol-2-yl)butyramide[128] (Table 16, Entry 18)



Following general procedure VII, *n*-butyramide (3 mmol, 261 mg) was used as the amide species and 2-aminothiazole (3.6 mmol, 361 mg) as the amine species. The *title compound* was recovered as beige solid (245 mg, 48% yield) after column chromatography (eluting with 1:1 Hex: EtOAc). Analytical data was consistent with that above.

3.08 *N*-Benzylpivalamide[108](Table 16, entry 19)



Following general procedure VII, 2,2,2-trimethylacetamide (3 mmol, 304 mg) was used as the amide species and benzylamine (3.6 mmol, 393 µL) as the amine species. The *title compound* was recovered as a brown oil (435 mg, 76% yield) after column chromatography (eluting with EtOAc/Hex 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ. 7.41 – 7.21 (5H, m, Ph), 5.94 (1H, br. s, N<u>H</u>), 4.44 (2H, d, *J* = 5.6 Hz, NHC<u>H</u>$_2$Ph), 1.23 (9H, s, 3 x C<u>H</u>$_3$)

^{13}C NMR (75 MHz, $CDCl_3$): δ. 178.3, 138.7, 128.7, 127.7, 127.5, 43.6, 38.7, 27.6.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1633 (C=O stretch)

HRMS(ESI-TOF) calcd for $[C_{12}H_{17}NOH]^+$: 192.1388. Found: 192.1397.

Use of 2,2,2-trifluoroacetamide and formamide (Chapter 3 Section 3.4.2.)

As with general procedure VII, formamide (40 µL, 1 mmol) and 2,2,2-trifluoroacetamide (113 mg, 1 mmol) were used as the amide species and benzylamine (131 µL, 1.2 mmol) as the amine species. After 5 hours, solvent was removed *in vacuo* and the crude conversions were determined by analysis of crude ^{1}H NMR spectra

Use of Secondary and Tertiary Amides (Chapter 3 Section 3.4.3.)

As with general procedure VII, *N*-methylacetamide **2.32** (76 µL, 1 mmol), DMAC **2.33** (93 µL, 1 mmol) or 4'methylacetanilide **2.30** (149 mg, 1 mmol) were used as the amide species and benzylamine (131 µL, 1.2 mmol) as the amine species. After 18 hours, solvent was removed *in vacuo* and the crude conversions were determined by analysis of crude ^{1}H NMR spectra

Synthesis of *n*-nonanoylisothiocyanate 3.09 (Chapter 3 Section 3.5.1)

To an oven-dried Schlenk was added KSCN (2 mmol, 194.4 mg), the vessel was put under vacuum and backfilled with argon, this process was repeated two more times. A solution of anhydrous acetone (6 mL) containing *n*-nonanoyl chloride was added to the vessel and the vessel was sealed and stirred at 40 °C for 2 hours. After this time the reaction was cooled to room temperature and the reaction mixture filtered under an argon atmosphere by cannula filtration. Subsequent removal of the solvent was carried out *in vacuo* and the crude product was analysed by ^{13}C NMR.

Synthesis of zirconocene diisothiocyanate ($Cp_2Zr(NCS)_2$)[129] 3.12 (Chapter 3 Section 3.5.1.)

Based on a modified literature preparation; [130] To an oven dried Schlenk tube was added Cp_2ZrCl_2 (2 mmol, 584 mg) and KSCN (4 mmol, 388 mg. Previously dried under heating and vacuum) and the Schlenk was put under vacuum and backfilled with argon, this process was repeated two more times. After this anhydrous acetone (5 mL) was added to the Schlenk and the reaction vessel was sealed and heated to reflux for 6 hours. After cooling to room temperature the reaction was cooled to room temperature and filtered under an argon atmosphere by cannula filtration. Subsequent removal of the solvent was carried out *in vacuo* and the crude product was analysed by ^{1}H and ^{13}C NMR.

^{1}H NMR (300 MHz, d8-PhMe): 5.53 (10H, s, Cp)

^{13}C NMR (75 MHz, d8-PhMe): 114.7

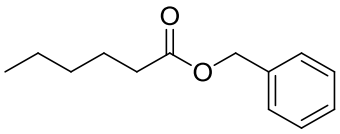
IR(neat): $\overline{\nu}$ (cm^{-1}) = 1987, 1011 (Cp) , 820 (Cp)

5.4 Chapter 4 Experimental Methods and Compound Characterisation

General Procedure VIII. Catalyst Screen and Optimisation*:* *n*-Hexanamide (57.7 mg, 0.5 mmol) was added to an oven dried Radleys carousel tube. To this solvent (0.25 or 0.5 mL), benzyl alcohol (appropriate volume), and the appropriate catalyst (5 or 10 mol% as appropriate) were added and the tube sealed and heated for 24 hours at reflux. The reaction mixture was allowed to cool to room temperature before the solvent was removed *in vacuo* with the crude reaction mixtures analysed by their ^{1}H NMR spectra.

General Procedure IX. *O*-Acylation of Alcohols with Amides: An oven dried Radleys carousel tube was charged with amide species (2 mmol), $Sc(OTf)_3$ (5 mol%, 49.3 mg) and heptane (2.0 mL), followed by the alcohol species (2.4 mmol). The reaction was then heated with stirring at either 100 or 125 ^{o}C (**Table 22** or **Table 23**) for 24 hours. After being allowed to cool to room temperature the solvent was removed *in vacuo* on a rotary evaporator and the crude reaction mixture was analysed by observing the ^{1}H NMR and ^{13}C NMR spectra. After which the crude reaction was purified either using a 20 mm x 50 mm plug of silica gel (eluting with DCM) or by column chromatography.

4.03. Benzyl hexanoate[131] (Table 22, Entry 1)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and benzyl alcohol (2.4 mmol, 248 μL) as the alcohol species. The *title compound* was recovered as a colourless oil (372 mg, 90% yield) after a silica gel plug (eluting with DCM).

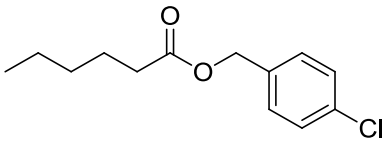
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.30 (5H, m, Ph), 5.12 (2H, s, $C\underline{H}_2Ph$), 2.36 (2H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_2C(O)$), 1.76 – 1.46 (2H, quin., *J* = 7.5 Hz, $CH_2C\underline{H}_2CH_2C(O)$), 1.42 – 0.95 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 0.89 (3H, t, *J* = 6.8 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 136.2, 128.7, 128.3, 66.2, 34.4, 31.4, 24.8, 22.4, 14.1.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1735 (C=O stretch), 1161 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{13}H_{18}O_2Na]^+$: 229.1204. Found: 229.1188.

4.06. 4-Chlorobenzyl hexanoate (Table 22, Entry 2)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and 4-chlorobenzyl alcohol (2.4 mmol, 342.2 mg) as the alcohol species. The *title compound* was recovered as a colourless oil (400 mg, 83% yield) after a silica gel plug (eluting with DCM).

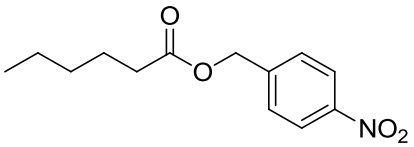
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 – 7.20 (4H, m, 4 x Aryl CH), 5.07 (2H, s, $C\underline{H}_2Ar$), 2.34 (2H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_2C(O)$), 1.61 (2H, quin, *J* = 7.5 Hz, $CH_2C\underline{H}_2CH_2C(O)$), 1.37 – 1.18 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 0.88 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 134.6, 134.1, 129.6, 128.7, 65.2, 34.2, 31.3, 24.6, 22.3, 13.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1735(C=O stretch), 1160 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{13}H_{17}O_2ClNa]^+$: 263.0815. Found: 263.0864.

4.07. 4-Nitrobenzyl hexanoate[132] (Table 22, Entry 3)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and 4-nitrobenzyl alcohol (2.4 mmol, 367.5 mg) as the alcohol species. The *title compound* was recovered as a light yellow oil (241 mg, 48% yield) after a silica gel plug (eluting with DCM).

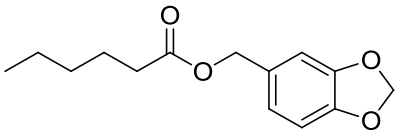
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (2H, dt, *J* = 8.8, 2.2 Hz, 2 x Aryl CH), 7.54 – 7.46 (2H, dt, *J* = 8.6, 2.1 Hz, 2 x Aryl CH), 5.19 (2H, s, $C\underline{H}_2Ar$), 2.38 (2H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_2C(O)$), 1.58 (2H, quin., *J* = 7.5 Hz, $CH_2C\underline{H}_2CH_2C(O)$), 1.39 – 1.19 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 0.96 – 0.82 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.4, 147.6, 143.5, 128.3, 123.8, 64.6, 34.1, 31.3, 24.6, 22.3, 13.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1737 (C=O stretch), 1520 (N-O asymmetric stretch), 1344 (N-O symmetric stretch), 1158 (C-O stretch).

HRMS(ESI-TOF) calcd for $[C_{13}H_{17}O_4Na]^+$: 274.1055. Found: 274.1042.

4.08. Piperonyl hexanoate (Table 22, Entry 5)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and piperonyl alcohol (2.4 mmol, 362.2 mg) as the alcohol species. The *title compound* was recovered as a pale yellow oil (369 mg, 74% yield) after a silica gel plug (eluting with DCM).

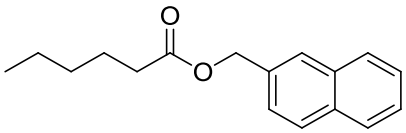
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.87 – 6.75 (3H, m, 3 x Aryl C<u>H</u>), 5.95 (2H, s, OC<u>H</u>$_2$O), 5.00 (2H, s, C<u>H</u>$_2$Ar), 2.32 (2H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_2C(O)$), 1.62 (2H, quin., *J* = 7.4 Hz, $CH_2C\underline{H}_2CH_2C(O)$), 1.47 – 1.08 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 0.87 (3H, t, *J* = 7.5 Hz, C<u>H</u>$_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.7, 147.8, 147.6, 129.9, 122.2, 109.0, 108.2, 101.2, 66.0, 34.3, 31.3, 24.6, 22.3, 13.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1732 (C=O stretch), 1162 (C-O stretch, ester)

HRMS(ESI-TOF) calcd for $[C_{14}H_{18}O_4Na]^+$: 273.1103. Found: 273.1098.

4.10. Naphthalen-2-ylmethyl hexanoate (Table 22, Entry 7)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and 2-naphthalenemethanol (2.4 mmol, 379.7 mg) as the alcohol species. The *title compound* was recovered as light brown oil (477 mg, 93% yield) after a silica gel plug (eluting with DCM).

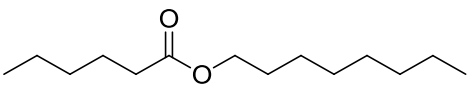
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.93 – 7.79 (4H, m, 4 x Aryl C<u>H</u>), 7.70 – 7.43 (3H, m, 3 x Aryl C<u>H</u>), 5.30 (2H, s, C<u>H</u>$_2$Ar), 2.40 (2H, t, *J* = 7.6 Hz, $CH_2C\underline{H}_2C(O)$), 1.86 – 1.56 (2H, m, $CH_2C\underline{H}_2CH_2C(O)$), 1.56 – 1.26 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 1.02 – 0.74 (3H, m, C<u>H</u>$_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 133.6, 133.2, 133.1, 128.4, 128.0, 127.8, 127.3, 126.3, 126.3, 125.9, 66.3, 34.4, 31.4, 24.7, 22.4, 14.0.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1733 (C=O stretch), 1163 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{17}H_{20}O_2Na]^+$: 279.1361. Found: 279.1368.

4.12. *n*-Octyl hexanoate[133] (Table 22, Entry 9)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and *n*-octanol (2.4 mmol, 377 µL) as the alcohol species. The *title*

compound was recovered as a colourless oil (417 mg, 91% yield) after a silica gel plug (eluting with DCM).

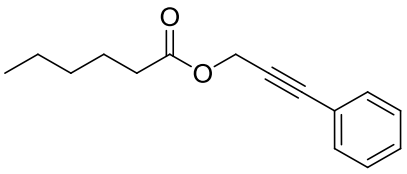
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.03 (2H, t, *J* = 6.7 Hz, $CO_2C\underline{H}_2CH_2$), 2.26 (2H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_2C(O)$), 1.68 – 1.42 (4H, m, 2 x alkyl $C\underline{H}_2$), 1.42 – 1.12 (14H, m, 7 x alkyl $C\underline{H}_2$), 1.12 – 0.76 (6H, m, 2 x $C\underline{H}_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 64.3, 34.3, 31.7, 31.3, 29.19, 29.17, 28.7, 25.9, 24.7, 22.6, 22.3, 14.0, 13.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1737 (C=O stretch), 1169 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{14}H_{28}O_2H]^+$: 229.2168. Found: 229.2161.

4.13. 3-Phenylprop-2-yn-1-yl hexanoate[131] (Table 22, Entry 10)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and 3-phenyl-2-propyn-1-ol (2.4 mmol, 299 μL) as the alcohol species. The *title compound* was recovered as pale yellow oil (376 mg, 82% yield) after a silica gel plug (eluting with DCM).

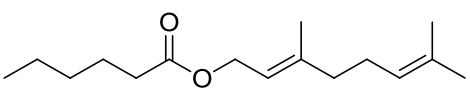
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51 – 7.40 (2H, m, 2 x Aryl CH), 7.40 – 7.26 (3H, m, 3 x Aryl CH), 4.91 (2H, s, $OC\underline{H}_2CC$), 2.37 (2H, t, *J* = 7.5 Hz, $C\underline{H}_2C(O)$), 1.84 – 1.46 (2H, m, $C\underline{H}_2CH_2C(O)$), 1.38 – 1.27 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 0.90 (3H, t, *J* = 6.7 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 131.9, 128.7, 128.3, 122.2, 86.4, 83.1, 52.6, 34.1, 31.3, 24.6, 22.3, 13.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1740 (C=O stretch), 1155 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{15}H_{18}O_2Na]^+$: 253.1204. Found: 253.1196.

4.14. Geranyl hexanoate (Table 22, Entry 11)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and geraniol (2.4 mmol, 299 µL) as the alcohol species. The *title compound* was recovered as a colourless oil (430 mg, 85% yield) after a silica gel plug (eluting with DCM).

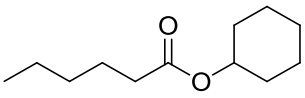
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.32 (1H, tt, *J* = 5.7, 2.8 Hz, $OCH_2C\underline{H}$), 5.07 (1H, dd, *J* = 6.6, 5.4 Hz, $C\underline{H}C(CH_3)_2$), 4.58 (2H, d, *J* = 7.1 Hz, $OC\underline{H}_2CH$), 2.29 (2H, t, *J* = 7.6 Hz, $C\underline{H}_2C(O)$), 2.15 – 1.96 (4H, m, $(CH_3)CC\underline{H}_2C\underline{H}_2CH$), 1.73 – 1.54 (11H, m, $(C\underline{H}_3)CCH_2$ $(C\underline{H}_3)_2CCH$ and $C\underline{H}_2CH_2C(O)$), 1.35 – 1.21 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 0.88 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 142.1, 131.8, 123.8, 118.4, 61.2, 39.5, 34.4, 31.3, 26.3, 25.69, 24.7, 22.4, 17.7, 16.5, 13.9.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1735 (C=O stretch), 1166 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{16}H_{28}O_2Na]^+$: 275.1987. Found: 275.1981.

4.15. Cyclohexyl hexanoate[134] (Table 22, Entry 12)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and cyclohexanol (2.4 mmol, 253 µL) as the alcohol species. The *title compound* was recovered as a colourless oil (335 mg, 84% yield) after a silica gel plug (eluting with DCM).

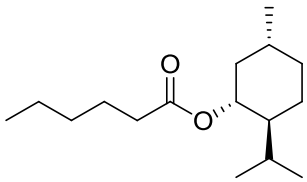
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.68 (1H, m, $OC\underline{H}(CH_2)$), 2.20 (2H, t, *J* = 7.5 Hz, $CH_2C\underline{H}_2C(O)$), 1.92 – 1.01 (16H, m, 5 x $C\underline{H}_2$ Cyclohexyl and 3 x $C\underline{H}_2$), 0.82 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 72.4, 34.8, 31.8, 31.4, 25.5, 24.9, 23.9, 22.4, 14.0.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1731 (C=O stretch), 1173 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{12}H_{22}O_2Na]^+$: 221.1516. Found: 221.1517.

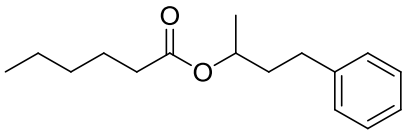
4.16. (1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl hexanoate[131] (Table 22, Entry 13)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and menthol (2.4 mmol, 375 mg) as the alcohol species. The *title compound* was recovered as a colourless oil (369 mg, 72% yield) after a silica gel plug (eluting with DCM).

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (1H, td, *J* = 10.9, 4.4 Hz, OC<u>H</u>(CH_2)CH), 2.20 (2H, t, *J* = 7.5 Hz,C<u>H</u>$_2$C(O)), 1.99 – 1.86 (1H, m, C<u>H</u>CH(CH_3)$_2$), 1.79 (1H, sept. d, *J* = 7.0, 2.8 Hz, CHC<u>H</u>(CH_3)$_2$), 1.67 – 1.50 (4H, m, C<u>H</u>$_2$$CH_2$C(O) and menthyl ring), 1.48 – 1.36 (1H, m), 1.34 – 1.19 (5H, m, CH_3C<u>H</u>$_2$C<u>H</u>$_2$ and menthyl ring), 1.05 – 0.76 (12H, m, menthyl ring), 0.68 (3H, d, *J* = 7.0 Hz, C<u>H</u>$_3$$CH_2$).
^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 74.0, 47.1, 41.1, 34.8, 34.4, 31.5, 31.4, 26.3, 24.9, 23.5, 22.5, 22.2, 20.9, 16.4, 14.1.
IR(neat): $\bar{\nu}$ (cm^{-1}) = 1732 (C=O stretch), 1173 (C-O stretch)
HRMS(ESI-TOF) calcd for $[C_{16}H_{30}O_2Na]^+$: 277.2144. Found: 277.2160.

4.17. 4-Phenylbutan-2-yl hexanoate[135] (Table 22, Entry 14)



Following general procedure IX, *n*-hexanamide (2.0 mmol, 230.4 mg) was used as the amide species and 4-phenylbutan-2-ol (2.4 mmol, 372 µL) as the alcohol species. The *title compound* was recovered as pale yellow oil (412 mg, 83% yield) after a silica gel plug (eluting with DCM).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.12 (5H, m, Ph), 5.05 – 4.86 (1H, m, OC<u>H</u>(CH_3)CH_2), 2.76 – 2.52 (2H, m, C<u>H</u>$_2$Ph), 2.29 (2H, t, *J* = 7.5 Hz,

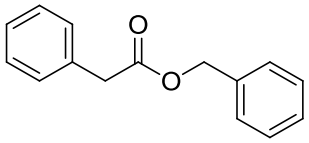
$CH_2C\underline{H}_2C(O)$), 2.03 – 1.72 (2H, m, $CH(CH_3)C\underline{H}_2$), 1.64 (2H, q, *J* = 7.4 Hz, $C\underline{H}_2CH_2C(O)$), 1.40 – 1.28 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 1.25 (3H, d, *J* = 6.3 Hz, $OCH(C\underline{H}_3)CH_2$), 0.91 (3H, t, *J* = 6.9 Hz, $C\underline{H}_3CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 142.1, 129.0, 128.9, 126.4, 70.7, 38.2, 35.2, 32.4, 31.9, 25.3, 22.9, 20.6, 14.5.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1731 (C=O stretch), 1174 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{16}H_{24}O_2H]^+$: 249.1855. Found: 249.1847.

4.19. Benzyl 2-phenylacetate[136] (Table 23, Entry 1)



Following general procedure IX, 2-phenylacetamide (2.0 mmol, 242.4 mg) was used as the amide species and benzyl alcohol (2.4 mmol, 248 µL) as the alcohol species. The *title compound* was recovered as a colourless oil (425 mg, 94% yield) after a silica gel plug (eluting with DCM).

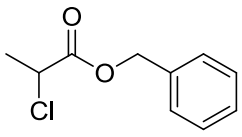
^1H NMR (300 MHz, $CDCl_3$): δ 7.42 – 7 27 (10H, m, 2 x $\underline{Ph}$), 5.17 (2H, s, $OC\underline{H}_2Ph$), 3.71 (2H, s, $PhC\underline{H}_2C(O)$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 135.9, 134.0, 129.4, 128.64, 128.59, 128.3, 128.2, 127.2, 66.7, 41.4.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1732 (C=O stretch), 1140 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{15}H_{14}O_2Na]^+$: 249.0891. Found: 249.0878.

4.20. Benzyl 2-chloropropionate[137] (Table 23, Entry 2)



Following general procedure IX, 2-chloropropionamide (2.0 mmol, 215.1 mg) was used as the amide species and benzyl alcohol (2.4 mmol, 248 µL) as the alcohol species. The *title compound* was recovered as a colourless oil (217 mg, 55% yield) after a silica gel plug (eluting with DCM).

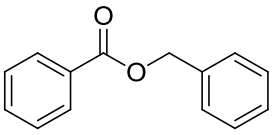
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 – 7.29 (5H, m, Ph), 5.22 (2H, CH_2Ph), 4.45 (1H, q, *J* = 6.9 Hz $CH_3(Cl)CH$), 1.71 (3H, d, *J* = 7.0 Hz, CH_3CH).

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 135.2, 128.7, 128.6, 128.3, 67.7, 52.5, 21.5.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1742 (C=O stretch), 1167 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{10}H_1O_2ClNa]^+$: 221.0345. Found: 221.0337.

4.21. Benzyl benzoate[136] (Table 23, Entry 3)



Following general procedure IX, benzamide (2.0 mmol, 242.4 mg) was used as the amide species and benzyl alcohol (2.4 mmol, 248 µL) as the alcohol species. The *title compound* was recovered as a colourless oil (331 mg, 78% yield) after a silica gel plug (eluting with DCM).

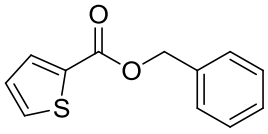
^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (2H, d, *J* = 7.3 Hz, 2 x Aryl CH), 7.58 (1H, t, *J* = 7.4 Hz, Aryl CH), 7.52 – 7.30 (7H, m, 7 x Aryl CH), 5.39 (2H, s, CH_2Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 136.1, 133.1, 130.2, 129.8, 128.6, 128.4, 128.3, 128.21, 66.7.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1715 (C=O stretch), 1266 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{14}H_{12}O_2Na]^+$: 235.0735. Found: 235.0729.

4.23. Benzyl thiophene-2-carboxylate[138] (Table 23, Entry 5)



Following general procedure IX, 2-thiophencarboxamide (2.0 mmol, 254.3 mg) was used as the amide species and benzyl alcohol (2.4 mmol, 248 µL) as the alcohol species. The *title compound* was recovered as a pale yellow oil (310 mg, 71% yield) after a silica gel plug (eluting with DCM).

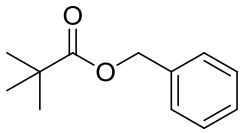
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (1H, dd, *J* = 3.8, 1.2 Hz, thiophene CH), 7.57 (1H, dd, *J* = 5.0, 1.2 Hz, thiophene CH), 7.49 – 7.31 (5H, m, Ph), 7.10 (1H, dd, *J* = 5.0, 3.8 Hz, thiophene CH), 5.36 (2H, s, C<u>H</u>$_2$Ph).

^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1, 135.9, 133.7, 132.7, 128.6, 128.3, 128.2, 127.8, 66.8.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1704 (C=O stretch), 1254 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{12}H_{10}O_2SNa]^+$: 241.0299. Found: 241.0290.

4.24. Benzyl pivalate[139] (Table 23, Entry 6)



Following general procedure IX, pivalamide (2.0 mmol, 254.3 mg) was used as the amide species and benzyl alcohol (2.4 mmol, 248 µL) as the alcohol species. The *title compound* was recovered as a light brown oil (150 mg, 39% yield) after a silica gel plug (eluting with DCM).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.28 (5H, m, <u>Ph</u>), 5.12 (2H, s, C<u>H</u>$_2$Ph), 1.24 (9H, s, 3 x C<u>H</u>$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 136.5, 128.5, 128.0, 127.7, 66.0, 38.8, 27.2.

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1727 (C=O stretch), 1140 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{12}H_{16}O_2Na]^+$: 215.1048. Found: 215.1060.

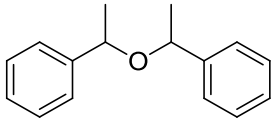
Use of Secondary and Tertiary Amides (Chapter 4 Section 4.4.3.)

As with general procedure IX, *N*-methylacetamide **2.32** (76 µL, 1 mmol), DMAC **2.33** (93 µL, 1 mmol) or 4'methylacetanilide **2.30**(149 mg, 1 mmol) were used as the amide species and benzyl alcohol (124 µL, 1.2 mmol) as the alcohol species. After 24 hours, the solvent was removed *in vacuo* and the crude conversions were determined by analysis of crude ^{1}H NMR spectra

Competition Reactions (Chapter 4 Section 4.5)

2-Phenylacetamide (1 mmol, 135.2 mg), ethyl hydrocinnamate (1 mmol, 176.4 µL) or hydrocinnamic acid (1 mmol, 150 mg), $Sc(OTf)_3$ (5 mol%, 24.6 mg) and *n*-heptane (1.0 mL), were added to an oven dried Radleys carousel tube, followed by benzyl alcohol (1.0 mmol, 103.3 µL). The reaction was then heated with stirring at 100 ^oC for 24 hours. After being allowed to cool to room temperature the solvent was removed in vacuo on a rotary evaporator and the crude reaction mixtures were analysed by their ^1H NMR spectra to determine the conversion of the reaction

Synthesis of symmetrical bis-(1-phenyl)ethyl ether 4.27 (Chapter 4 Section 4.6**)**



Triflic acid (44.2 µL, 0.5 mmol) was added to a stirring solution of 1-phenylethanol (1.207 mL, 10 mmol) in $MeNO_2$ (15 mL). After 4 hours at room temperature the reaction solvent was removed *in vacuo* and the crude reaction mixture was analysed by ^1H NMR spectroscopy. The *title compound* was recovered as a colourless oil (1.81 g, 80% yield) after column chromatography (eluting with Pet. Ether/Et_2O, 50:1).

^1H NMR (300 MHz, $CDCl_3$): Observed as a mixture of diastereomers ~ 5:1 δ 7.49 – 7.16 (m, 10H), 4.57 (q, *J* = 6.4 Hz,C<u>H</u>CH_3, 1H, minor product (*meso*)), 4.29 (q, *J* = 6.5 Hz, C<u>H</u>CH_3, 1H, major product (*dl*)), 1.50 (d, *J* = 6.5 Hz, CHC<u>H</u>$_3$6H, minor product (*meso*)), 1.43 (dd, *J* = 6.5 Hz, 6H, major product (*dl*)).

^{13}C NMR (75 MHz, $CDCl_3$): Observed as a mixture of diastereomers ~ 5:1 δ 144.3 (minor isomer), 144.2 (major isomer), 128.5 (major isomer), 128.3 (minor isomer), 127.5 (major isomer), 127.2 (minor isomer), 126.4 (major isomer), 126.3 (minor isomer), 74.7 (major isomer), 74.4 (minor isomer), 24.8 (minor isomer), 23.1 (major isomer)

IR(neat): $\bar{\nu}$ (cm^{-1}) = 1086 (C-O stretch)

HRMS(ESI-TOF) calcd for $[C_{16}H_{18}ONa]^+$: 249.1255. Found: 249.1245.

Use of symmetrical dibenzylethers

As with general procedure IX, *n*-hexanamide (0.5 mmol, 57 mg) was used as the amide species with either bis-(1-phenyl)ethyl ether **4.27** (0.5 mmol, 113 mg) or dibenzyl ether **4.04**(0.5 mmol, 95 µL) and H_2O (0.25 mmol) added as well.

NMR studies

n-Hexanamide (69.2 mg, 0.6 mmol) was added to a Wilmad 5mm width NMR tube. To this $CDCl_3$ (0.6 mL) and *n*-octanol (157 µL, 0.6 mmol) were added and the tube sealed. The ^1H and ^{13}C NMR spectra were then obtained on a Bruker 400 MHz NMR spectrometer at 25 °C. Following this $Sc(OTf)_3$ was added in increasing amounts, the tube was sealed and shaken until homogeneous and the ^1H and the ^{13}C NMR spectra were obtained.

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Appendix

Publications to date

1. Enzyme catalysed transamidation of primary amides – B.N. Atkinson, H. Nicholls, J.M.J. Williams, *Manuscript in preparation*

2. Zirconium catalyzed amidation reactions – B.N. Atkinson, A.R. Chhatwal, D.P. Van der Waals, J.W. Walton, J.M.J. Williams, *Manuscript in preparation*

3. Scandium triflate catalyzed synthesis of esters using primary amides – B.N. Atkinson, J.M.J. Williams, *Tetrahedron Lett.*, **2014**, *55*, 6935-6938 (Corresponding Author)

4. Dimethylsulfoxide as an N- methylation reagent for amines and aromatic nitro compounds (Highlight) – B.N. Atkinson, J.M.J. Williams, *ChemCatChem.* **2014**, *6*, 1860

5. Ruthenium- catalyzed remote electronic activation of aromatic C-F bonds – A.J.A. Watson, B.N. Atkinson, A.C. Maxwell, J.M.J. Williams, *Adv. Synth. Catal.* **2013**, *355*, 734

6. Transamidation of primary amides with amines catalyzed by zirconocene dichloride – B.N. Atkinson, A.R. Chhatwal, H.V. Lomax, J.W. Walton, J.M.J. Williams, *Chem. Commun.* **2012**, *48*, 11626

7. Transamidation of primary amides with amines using hydroxylamine hydrochloride as an inorganic catalyst – C.L. Allen, B.N. Atkinson, J.M.J. Williams, *Angew. Chem. Int. Ed.* **2011**, *51*, 1383 (Highlighted paper in *Synfacts*, **2012**, *8*, 326)